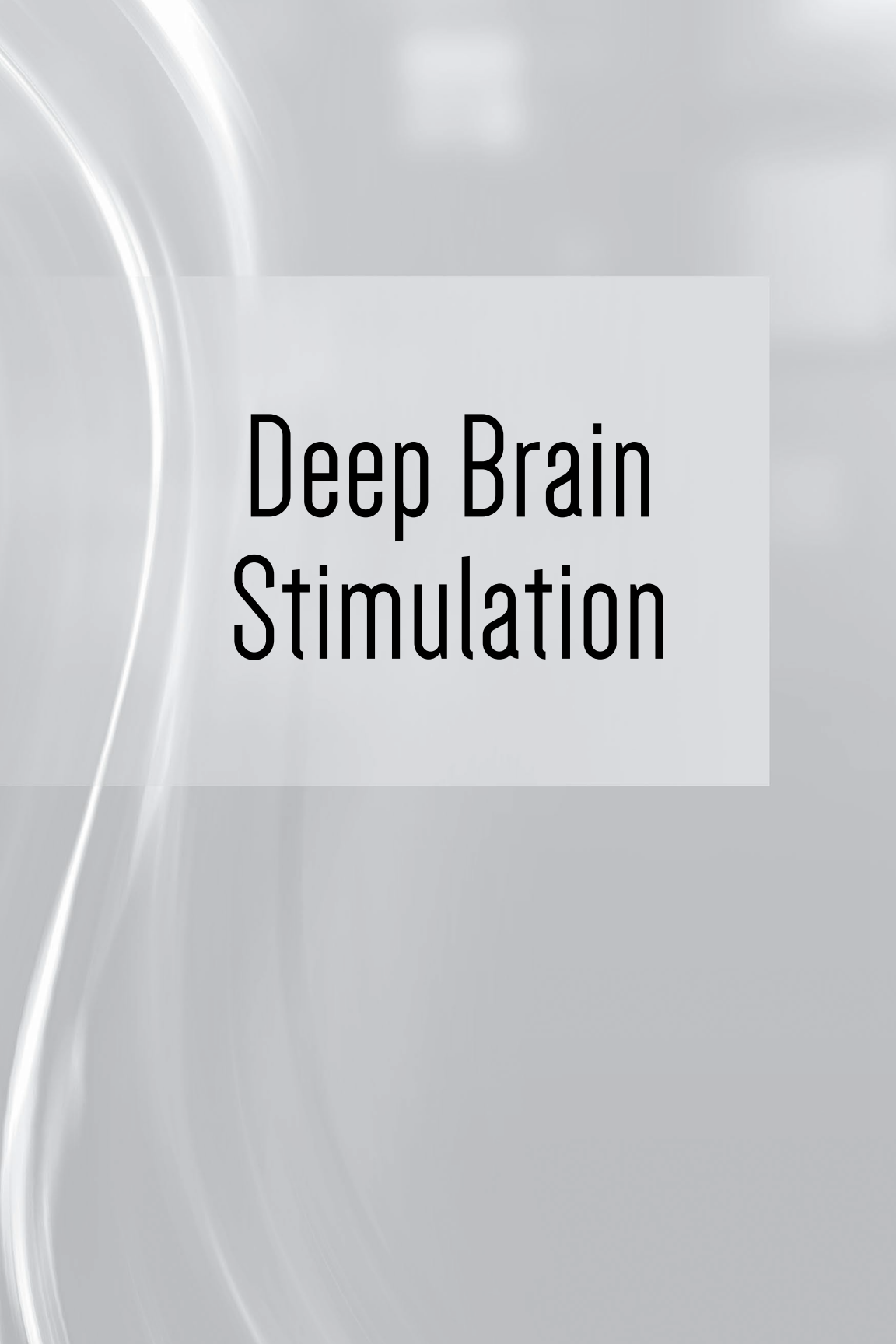




Deep Brain Stimulation



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Deep Brain Stimulation

Indications and Applications

edited by

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Preface

The success of deep brain stimulation (DBS) as a restorative neurosurgical treatment for certain intractable, neurologically based movement disorders has led to its consideration for a rapidly expanding list of neurologic and psychiatric conditions. Many of these newer applications are at the investigational stage but hold promise as an efficacious means of managing a wide variety of treatment-resistant conditions. These advances have led to increased and expanded efforts to understand the molecular, neural network, and behavioral effects of DBS. Clinical and preclinical DBS research is focused on improving patient care by deepening our understanding of pathologic and normal brain function. It encompasses not only investigations of the effects of DBS on neural activity, patient behavior, and outcomes, but also methods of improving electrode implantation and surgical targeting, techniques to trace the neurochemical and neural network effects of stimulation, engineering improved electrodes and new stimulation devices, such as closed-loop systems that use physiologic feedback to adjust stimulation delivery, and the design and implementation of carefully controlled clinical trials. Such wide-ranging yet integrated research and development efforts require input from the medical disciplines of neurology, neurosurgery, and psychiatry, but also from a variety of scientific disciplines such as engineering, computer science, applied mathematics, imaging science, neurochemistry, neurobiology, neurophysiology and experimental and behavioral psychology.

The need for an interdisciplinary approach to DBS research thus draws on the expertise of those who may be unfamiliar with the clinical application of DBS or with the science behind it or both. This book is intended as a handbook or introduction to the field for professionals and students who are new to DBS or to particular aspects of it. It grew out of work conducted at the Mayo Clinic Neural Engineering Laboratory, which is investigating DBS mechanisms and ways to improve its clinical application and outcomes. For students in graduate programs or medical school, we hope this

book serves not only as an overview of the field but as a source of inspiration to contribute to it. We hope that established clinicians and seasoned scientists from related and disparate fields, whose expertise is needed in basic or translational DBS research, will find it a useful resource.

We have divided the book into three major sections. The **Introduction** serves as an overview of the fundamentals of DBS. **Chapter 1** covers the somewhat tumultuous history of early uses of DBS in psychiatry to its present day applications to both neurologic and psychiatric disorders and provides the basic mathematics of stereotactic surgery, without which DBS would not be possible. It also introduces the reader to the standard DBS surgical procedure and discusses ethical issues that should be taken into account in clinical DBS practice.

To appreciate the therapeutic effects of clinical DBS, it is necessary to understand something about the electrophysiological basis of electrical stimulation and its effects on neural tissue. Thus, **Chapter 2** explores the principles of extracellular stimulation, neural excitability, interactions at the electrode-electrolyte tissue interface, and the electrochemical properties that affect the safety and therapeutic benefits of clinical DBS.

It is understood that DBS has effects not only at the stimulating electrode implantation target site but also in areas distal to the stimulated target that are structurally or functionally connected to it. To help the reader understand how neural networks are affected by pathology and DBS, **Chapter 3** reviews the basal ganglia-corticothalamic circuitry as represented by Parkinson's disease. It will help readers appreciate the complexity of the circuitry and its implications for DBS target structures that are part of it.

Neuroimaging is critical not only to surgical targeting of deep brain structures but also to research on the circuitry and neural network effects of DBS. **Chapter 4**, on imaging in DBS, provides a brief overview of fundamentals of magnetic resonance imaging and positron emission tomography and reviews the use of and advances in functional brain imaging for the study of DBS-evoked global changes in neural activation. **Chapter 5** reviews critical ethical issues in the use of DBS in patients with conditions commonly treated by DBS and those with conditions for which DBS is in the investigational stage.

The second section of the book, **Clinical Applications**, explores clinical impact of DBS for a wide range of neurologic and psychiatric conditions. Each of **Chapters 6 through 15** describes a specific disorder; the deep brain structures that have been targeted to treat it, the rationale behind the DBS target choices, and clinical outcomes to-date. **Chapter 16** describes the use of electrical stimulation to restore function following spinal cord injury. Although it does not involve DBS, specifically, it shares the goal of functional restoration by means of electrical stimulation. The chapter reviews the present progress in applying electrical stimulation systems that are transcutaneous and those that stimulate peripheral nerves or muscle fibers, as well as implanted epidural and intraspinal systems that stimulate the spinal cord directly.

The last section, **Research on Mechanisms of DBS and Neuromodulation**, has six chapters that cover theories and methods for studying the neurobiological effects of DBS. **Chapter 17** reviews past and present hypotheses about the neuronal, metabolic, and physiologic mechanisms that underlie the therapeutic effects of DBS. **Chapter 18** focuses on the understudied role of astrocytes and their potential contribution to DBS effects and mechanisms. **Chapter 19** reviews the methods of measuring real-time DBS-evoked neurochemical changes in the brain, specifically in vivo voltammetry. These alterations in neurotransmitter release hold promise as a source of physiologically relevant information for future closed-loop feedback devices, which could fundamentally alter the delivery of DBS to minimize adverse effects and accentuate therapeutic outcomes. **Chapter 20** provides the reader with an appreciation for the intricacies and complex design considerations of creating DBS stimulating and recording electrodes, including their size, shape, biocompatibility, electronic impedance, and surface chemistry. A biocompatible and durable chronic recording electrode can be considered the holy grail of future devices designed to use neurochemical or neurophysiologic feedback to control stimulation delivery. An explanation of closed-loop control systems for DBS, including electrophysiologic and neurochemical techniques and mathematical modeling, is provided in **Chapter 21**. The final chapter in the book, **Chapter 22**, explores another avenue of

neuromodulation: advances in molecular and cellular restoration that rely on biologic therapies to repair central nervous system dysfunction. It focuses primarily on spinal cord injury, but serves to alert the reader to the spectrum of scientific efforts in promoting functional restoration of central neural structures.

We would like to thank our contributors, each of whom has brought his or her individual expertise and experience to the task. Together we hope this book serves to introduce the reader to the clinical and basic science foundations and the advances and challenges of DBS, as well as to its history and its future as a means of advancing improved patient care through neuromodulation.

Kendall H. Lee, MD, PhD, Editor

Penelope S. Duffy, PhD, and Allan J. Bieber, PhD, Co-editors

PART I
INTRODUCTION TO DEEP BRAIN
STIMULATION



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Chapter 1

Overview of the History and Application of Deep Brain Stimulation

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INTRODUCTION

The current era of functional neuromodulation offers immense opportunity for minimally invasive surgical treatment of certain debilitating neurologic and psychiatric disorders. As its name implies, the goal of functional neuromodulation is to alter or “modulate” neuronal activity so as to restore function. While pharmacology and invasive surgical approaches (e.g., targeted ablation of brain tissue) can be considered “neuromodulatory,” the term today is generally applied to techniques that alter local and distal neuronal activity through electrical pulses emitted by implanted electrodes in a neural target site. Deep brain stimulation (DBS), the most common of these approaches, involves implanting electrodes into targeted structures located deep within the brain.

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Other forms of neural stimulation include stimulation of the cerebral cortex (e.g., motor cortex stimulation for intractable pain), and spinal cord stimulation, currently under investigation as a treatment for spinal cord injury.

By the early 2000s, DBS had become an established restorative therapy for motor system disorders, such as Parkinson's disease (PD) [1], tremor [2], and dystonia [3]. Today, it is being investigated as a viable treatment for other neurologic disorders such as epilepsy [4–6], chronic pain [7, 8], and Tourette's syndrome [9–11]. DBS has also been investigated as a means of treating certain psychiatric disorders such as obsessive-compulsive disorder [12, 13], and major depression [14–16], and for cognitive disorders such as the memory dysfunction that can occur with degenerative, dementing conditions like Alzheimer's disease [17].

The success of DBS for PD, tremor, and dystonia raised the possibility of its wider application and generated increased investigation into its underlying mechanisms, which to date remain elusive. A better understanding of the complexity of the neural circuitry effects of DBS would shed light not only on its therapeutic mechanisms but also on normal brain function and its dysfunction in the disease states for which DBS is effective. Among the challenges for this research is the fact that the pathophysiology and the neural network activity involved in the disorders treated by DBS remain largely unknown.

Recent developments in neuroimaging and neurochemical monitoring are adding new insights into the disease-specific nature of impaired brain circuitry and effects of neurostimulation. These insights are also helping to advance the next generation of functional neuromodulation therapies and devices. This chapter will set modern functional neuromodulation and neurostimulation within the context of the history of stereotactic and functional neurosurgical procedures and recent DBS applications. As clinical and basic scientific investigations probe the modulatory effects of neurostimulation our knowledge and potential to treat these disorders is rapidly expanding. Indeed, this current era of neurostimulation may provide the key that unlocks many of the mysteries surrounding the biological basis of impaired motor, emotional, and cognitive neurocircuitry.

A number of recent reviews in the literature have covered the turbulent history of discovery, early abandonment, and recent

revitalization and development of DBS [18–23]. However, they have not specifically addressed the mathematics of stereotaxic neurosurgery, the evolution of stereotaxic instrumentation, and the early development of novel innovative neurosurgical procedures, without which modern application of DBS would not have been possible. Here, following a review of the history of brain stimulation, we provide an overview of the key technological and methodological innovations that originated in the eighteenth century and continue today to advance and extend functional DBS neurosurgery.

A BRIEF HISTORY OF THERAPEUTIC BRAIN STIMULATION

Deep Brain Stimulation for Movement Disorders

The concept of stimulating the human brain with electrical pulses as a treatment for disease had its beginnings in the mid-twentieth century. In 1969 a pioneer of the technique, Spanish physician Jose Delgado (1915–2011), discussed the ethical implications of his research in *Physical Control of the Mind: Toward a Psychocivilized Society* [24]. There he reviewed not only techniques to implant intracranial electrodes in humans but also his view of their potential therapeutic and diagnostic use in psychological disorders. It is important to place early efforts at stimulating the brain within the larger context of neurosurgical intervention for psychiatric disorders, one of which was lobotomy, a technique ultimately abandoned as damaging and unethical, but which remained in the public mind as a poisoned exemplar of all that is wrong with neurosurgical treatment for psychiatric conditions.

The earliest investigators of what became DBS were interested in brain stimulation as a therapy for psychological disorders. These included Russian neurophysiologist and neuroscientist Natalia Petrovna Bekthereva (1924–2008) at the Leningrad Institute of Experimental Medicine and the Academy of Medical Sciences of the USSR, who in the early 1960s was the first to use chronic depth electrostimulation as a therapy for motor disorders [25]; the Norwegian psychiatrist and neurophysiologist Carl Wilhelm Sem-Jacobsen (1912–1991), who completed a fellowship

at Mayo Clinic in 1955 and implanted depth electrodes to record and stimulate neural activity in patients with epilepsy and psychiatric disorders [26]; and American neurosurgeon Irving S. Cooper (1922–1985) who pioneered chronic stimulation of the cerebellar cortex for cerebral palsy, epilepsy, and spasticity in 1972 [27].

During his career, Cooper also developed several innovative techniques for the surgical management of PD and other movement disorders [27]. His keen interest in the physiology of movement disorders was kindled during medical training at George Washington University in Washington, D.C., and during his earning of a doctor of philosophy at Mayo Clinic through the University of Minnesota. He was also a neurosurgery resident at Mayo Clinic from 1948 until 1951, but it was when he joined the faculty at New York University Medical School and surgical staff at St. Barnabas (1954–1977) that he made a startling discovery. During a subtemporal approach for a cerebral pedunculotomy, a then accepted treatment for PD, he was forced to abort the pedunculotomy because of an inadvertent surgical injury to the anterior choroidal artery. Much to Cooper's surprise and his and the patient's unanticipated good fortune, the patient awoke from anesthesia to find the tremor and rigidity abolished without any residual hemiparesis. This serendipitous outcome lead Cooper to correctly hypothesize that the ligation of the anterior choroidal artery resulted in a small stroke in the thalamus, which was able to abolish tremor without hemiparesis. The thalamic area affected was eventually determined to be the ventral intermediate nucleus of the thalamus, a principal DBS target for tremor today.

This discovery created a paradigm shift in concepts of movement disorders. At the time, medical consensus held that lesioning the brain for treatment of tremor would cause paralysis, but Cooper's work led to the surgical innovation of ablating tissue within the basal ganglia thalamocortical complex and particularly, within the thalamus for movement disorders associated with PD. Although Cooper's initial techniques were mostly ablative, he also developed chemopallidectomy and later cryothalamectomy (surgical freezing) as a surgical "lesioning" technique for primary control of PD tremor.

However, the observation that chronic electrical stimulation demonstrated effects similar to thalamotomy led Cooper to use

DBS in the thalamus, including the internal capsule (a site that affects a variety of nuclei in the basal ganglia thalamocortical complex), for various types of movement disorders [28]. In fact, it is in the Methods section of his seminal 1980 paper that the term “deep brain stimulation” first appeared in the literature with the phrase, “Medtronic deep brain stimulation (DBS) electrodes were inserted by the Cooper stereotactic technique”

Around the same time that Cooper was developing these neurosurgical approaches, Medtronic Inc. (Minneapolis, Minnesota) established a neurological division with a focus on the development of DBS for chronic pain. To-date Medtronic has manufactured state-of-the-art devices for use in DBS for all FDA-approved treatments of neuropsychiatric disabilities.

The main applications for DBS during the 1970s and 1980s were for chronic pain, which accounts for the paucity of papers on DBS for PD and other movement disorders during that time. The surgical treatments for PD were then still in their infancy and largely untested. As early as 1954 during surgery for psychiatric disorders, it had been found that stimulating certain structures of the brain, such as the motor cortex, reduced pain. In surgical lesioning procedures, electrical stimulation with externalized stimulators sometimes preceded actual lesioning of those stimulated areas. These early intraoperative observations that electrical stimulation had beneficial effects lent considerable interest in the possibility that DBS might be effective in treating chronic pain [29].

In 1987 Alim-Louis Benabid (1942-), a French neurosurgeon, and Pierre Pollack, a neurologist and their colleagues in the Department of Neurosurgery at Grenoble University, La Tronche, France, made a breakthrough discovery that helped bring DBS to where it is today. Their 1987 publication “Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease” marked the inauguration of DBS as an effective neurosurgical method for treating movement disorders associated with PD [30]. They found that DBS at frequencies higher than 100 Hz ameliorated tremor, and in essence showed that electrical stimulation of the brain could safely mimic surgical ablation (see [31]). In a 1993 publication they identified and confirmed the nucleus of Jules Bernard Luys (presently referred to as the subthalamic nucleus [32]) as an optimal target

for DBS treatment of tremor [33]. The success of stimulation of that target constituted the coup de grâce for ablation techniques like posteroventral pallidotomy. This ushered in the birth of modern DBS neurological therapy for movement disorders and paved the way for its use in other disorders.

The Emergence of DBS for Psychiatric Disorders

Considering the tumultuous history of the development and application of neurosurgical approaches to psychiatric disorders, it should come as no surprise that applying electrical stimulation to the brain to treat conditions such as refractory depression and obsessive-compulsive disorder has engendered both public and clinical resistance. However, the continued success of DBS for movement disorders and other neurologic conditions has inspired investigations into its potential use as a novel, relatively noninvasive, more focused, and reversible treatment strategy for certain psychiatric conditions.

The disease burden of treatment-resistant mental illness for the individual, their family, and society and the potential to relieve it through neuromodulation technologies, demands that we carefully and methodically explore these therapeutic options with the highest degree of scientific rigor. Developing an appreciation of the somewhat tainted history of psychiatric neurosurgery will help to ensure that we avoid repeating past errors and safeguard patients and families. In doing so, it is also important to remain mindful of the significant differences that exist between the medicine of today and the early days of psychosurgery.

Psychiatric neurosurgery was introduced in an era devoid of psychoactive medications in which the only treatment option available was institutionalization. The desperate need for alternatives to incarceration and physical restraint needs to be appreciated in the context of the limitations of medical science at the time [34].

An important catalyst for the emergence of psychosurgery came in the 1930s with John Fulton's (1899–1960) investigations of how specific portions of the cerebral cortex modulated behavioral and physiological function. In 1935 Fulton and his colleague,

Carlyle Jacobsen, reported that bilateral removal of the frontal lobes profoundly reduced the expression of anxiety and “frustrational behavior” in chimpanzees (see [34–36]). Fulton and Jacobsen’s results are believed to have inspired the Portuguese neurologist António Caetano de Abreu Freire Egas Moniz (1874–1955) to surgically treat anxiety states in human patients. He also developed cerebral angiography, a technique allowing visualization of blood vessels in and around the brain. He is regarded as one of the founders of modern psychosurgery, having developed the leucotomy, a surgical procedure known better, and somewhat infamously, as frontal lobotomy. He went on to become the first Portuguese national to receive a Nobel Prize in 1949 “for his discovery of the therapeutic value of leucotomy in certain psychoses” (shared with Walter Rudolf Hess (1881–1973), a Swiss physiologist who mapped the areas of the brain involved in the control of internal organs).

Having attended the 1935 International Neurological Congress in London where Fulton and Jacobsen presented their primate work, Moniz enlisted Portuguese neurosurgeon Almeida Lima (1903–1985) to perform the first frontal leucotomy on a human subject (see [34, 37]). During this surgical procedure the fiber tracts from the frontal lobes were destroyed with an injection of alcohol [38]. In 1936, Moniz reported on the first human prefrontal leucotomy [39], and subsequently he devised the leucotome for use in the procedure [40]. He judged the results acceptable in the first 40 or so patients he treated, claiming, “Prefrontal leucotomy is a simple operation, always safe, which may prove to be an effective surgical treatment in certain cases of mental disorder.”

Interestingly, the other key figure in the audience at Fulton and Jacobsen’s presentation was American psychiatrist Walter Jackson Freeman II (1895–1972). In September 1936, Freeman, together with neurosurgeon James W. Watts (1904–1994), started their prefrontal lobotomy program at George Washington University using X-ray guidance and skeletal landmarks to locate the white matter tracts of interest. However, borrowing from a technique pioneered in 1937 by Italian psychiatrist and neurosurgeon Amaro Fiamberti (1895–1972) (see [41]), Freeman soon streamlined this procedure, introducing the transorbital leucotomy in 1946.

This now infamous technique involved inserting an ice pick underneath the eyelid through the roof of the orbit and maneuvering it appropriately to sever the desired fiber tracts [34], the key “advantage” of which was that it was a simple enough procedure that it could be performed in almost any hospital by a qualified neurosurgeon. However, it is worth noting that, despite the fact that Freeman had no formal surgical training, over a period of four decades he had personally performed as many as 3,439 lobotomy surgeries in 23 states of which 2,500 were his transorbital procedure [38]. The period between 1945 and 1955 saw approximately 50,000 lobotomies performed in the U.S. and intense media support for the procedure and for the work of such figures as Moniz and Freeman [38, 42]. One of Freeman’s more famous patients was Rosemary Kennedy, the sister of Senator and later President John F. Kennedy.

Over the course of the use of transorbital lobotomies, which began in the mid-1940s and continued into the early 1960s, it became apparent that many patients never fully recovered from the procedure, and that at least 15% died from complications from the surgery [43]. The resulting public abhorrence combined with clinician timidity at the “bluntness” of this surgical technique and the advent of antipsychotic medications such as chlorpromazine, marketed as an effective antipsychotic drug, caused the procedure to fall out of favor by the mid-twentieth century.

Despite the development of effective pharmacotherapies, Freeman remained a strong proponent of the frontal lobotomy until his death in 1972 [34, 38]. In 1974 the United States Congress considered a ban on psychosurgery. The National Commission for Protection of Human Subjects of Biomedical and Behavioral Research was part of the National Research Act of 1974 [44]. Although the driving force behind this body was to institute a ban on psychosurgery, their investigation provided sufficient evidence for the efficacy of modern procedures, such as the cingulotomy and anterior capsulotomy, which led instead to the call for further research into similar treatments [34]. Today, within the framework of neuromodulation technologies such as DBS, we are beginning to see a renaissance of neurosurgical intervention for severe psychiatric disorders [38, 45–48], which is addressed in more detail in Chapters 9, 10 and 11.

THE MATHEMATICS OF STEREOTACTIC NEUROSURGERY

The Development of Stereotactic Coordinate Systems

The modern era of functional neurosurgery would not have been possible without the development of the mathematical calculations and tools that enabled precise stereotactic targeting of deep brain structures with electrodes and devices such as the stereotaxic head frame that made such surgery possible. Because the brain cannot be palpated through the skull, functional neurosurgery relies on the external localization of targeted structures deep within the brain that are not visually accessible. It requires a map or brain atlas that identifies the location of internal structures based on external cranial landmarks. Through an external reference system of spatial coordinates, stereotactic instrumentation solves the problem of pinpointing such structures in three-dimensional (3D) space and thus allows precise guidance of surgical instruments, radiation beams, or electrodes into predetermined brain targets through small burr holes in the skull.

All surgical stereotactic systems are based on some mathematical system of 3D spatial coordinates and some system of achieving controlled movement along defined geometric axes. The history of stereotaxic navigation begins in seventeenth century France when lawyer and mathematician Pierre de Fermat (1601–1665) and philosopher and mathematician Rene Descartes (1596–1650) independently recognized that a system comprised of two perpendicular lines could be used to identify any point within a plane [49]. The distances along each of these lines (the x - and y -axes) from the point of origin to a specific point along the plane are given as an ordered pair of numbers or coordinates that is unique to that point in space. This rectangular coordinate system is called Cartesian, in honor of Descartes. With the addition of the third dimension (the z -axis), each location in space can be uniquely and quantitatively defined by its x , y , and z coordinates, a system still in use today.

The Cartesian system is composed of perpendicular lines (the x -, y -, and z -axes) from the point of origin (i.e., the intersection of the axes, where each axis is usually assigned a value of 0). The Polar system, introduced independently by the Flemish Jesuit

and mathematician Gregoire de Saint-Vincent (1584–1667) and the Italian mathematician Bonaventura Cavalieri (1598–1647) in the mid-seventeenth century, localizes a point in space by specifying its distance and direction from a point of origin (the fixed point or “pole”), that is, a radius and one or more angles perpendicular with respect to each other [50]. The Polar and Cartesian systems are mathematically equivalent, and one may convert the coordinates of one system to those of the other by the following formulas: $x = r \sin \theta \cos \phi$, $y = r \sin \theta \sin \phi$, $z = r \cos \theta$.

The Evolution of Stereotactic Instrumentation

Although the mathematics for stereotactic navigation were available in the late 1600s their use in the development of stereotactic equipment did not appear until the nineteenth century when the need arose. Some critical experiments in the 1860s, notably by two young German physicians, Eduard Hitzig (1838–1907) and Gustav Theodore Fritsch (1838–1927), were necessary to alter the prevailing understanding of brain function, which in turn would invigorate the development of investigatory brain devices. Their 1870 publication [51] broke with the traditional view that the brain surface was non-excitabile or that it responded only en masse to stimulation (i.e., Flourens’s holistic theory of equivalence of excitability). Their groundbreaking studies showed that galvanic stimuli of a few discrete areas on the dog brain produced contraction of muscles on the opposite side of the body. Thus, stimulation experiments, transection, and ablation of tissue in the central nervous system became important methods for exposing the relationships between brain anatomy and muscle function and later, for tracing fiber tracts. Initially, knives and picks were mounted on rack and pinion devices, and under micrometer control, were inserted at predetermined depths into brain tissue. These devices were utilized for crude brain surgery until at the turn of the twentieth century, the German physician and surgeon Frederick Trendelenburg (1844–1924) developed the myelotome, a lesion-making device that consisted of a mounted knife fixed onto a multi-jointed and pivoted frame that could be moved about in all planes.

These early rudimentary devices lacked precision, accuracy, and reproducibility. However in 1873, working in Carl Ludwig's laboratories in Leipzig Germany, the physiologist Charles Dittmar (1843–1917) was the first to report the use of guided probes into the medulla oblongata of animals [52]. Then in 1889, Demitri Zernov, a Russian anatomist at Moscow University, developed a rudimentary frame instrument called the “encephalometer,” using polar coordinates and an arc-based guiding mechanism to guide a probe to a specific brain location [53]. The apparatus was used on at least three occasions in human surgery, mainly in surface topography for localization of the cranial sutures and cerebral sulci.

In 1903 physician and neurosurgeon Victor Horsley (1857–1916) and surgeon, physiologist, and long-term collaborator Robert Clarke (1850–1926) introduced a new apparatus that used the Cartesian coordinate system and cranial landmarks to allow them to introduce lesions at specific locations within the cerebellum of monkeys with quasi-mathematical precision. James Swift, a machinist at Palmer and Company in London, was given the task of constructing a rectangular stereotaxic “machine” designed by Clarke. Although initially published as a short report [54], it was finally described in detail five years after construction [55]. This so-called rectilinear stereotaxic instrument allowed a biopsy needle or probe to be maneuvered in longitudinal or vertical directions by linear displacement of the stereotaxic electrode carrier. Although the machine was used in only three experimental studies, it made possible for the first time accurately targeted lesions, local injection of drugs, and recording of location-specific electrical activity. Interestingly, around 1918 Aubrey Thomas Mussen (1873–1975), who published the first cytoarchitectural stereotaxic atlas, also had made a frame based on a translational system and intended for human use, although it was never actually applied in surgery [56, 57]. Both of these systems relied on external cranial landmarks and thus had to account for the variability of such skull-based landmarks across humans. Clinical application of stereotactic head-frames had to wait until some form of visualizing internal brain landmarks was possible.

The initial brain imaging techniques, which enabled visualization of the brain inside the skull, relied on displacement of

cerebrospinal fluid in the ventricles and included ventriculography, developed between 1918–19 by Walter Dandy, and pneumoencephalography, which was a radiographic visualization of the fluid-containing structures of the brain after cerebrospinal fluid had been withdrawn and replaced by air, oxygen or helium [58]. These methods finally made it possible to use patient-specific internal landmarks such as the anterior and posterior commissures to estimate the location of other intracranial structures. Although these techniques were poorly tolerated by patients, the contemporary era of stereotactic-based functional neurosurgery in humans was thus ushered in.

In 1947 Ernst Spiegel (1885–1985), a neurologist, and Henry Wycis (1911–1972), a neurosurgeon, introduced a novel stereotactic system and neurosurgical techniques that made use of a 3D Cartesian coordinate-based stereotactic head frame for humans [59] with intracranial landmarks defined by pneumoencephalography. These human head frames were initially designed to lesion specific intracranial nuclei, a procedure which required precise stereotactic coordinates. Based on their work, Spiegel and Wycis published one of the first and most comprehensive stereotactic atlases of the human brain in 1952 [60].

There are numerous designs for modern stereotactic systems, including: (1) translational systems; (2) arc-centered systems; (3) focal point systems; (4) polar coordinate systems; (5) burr hole-mounted devices; (6) phantom target systems; (7) a system of interlocking arcs; (8) computer-based systems; and (9) the so-called “frameless” systems. Arc-centered systems, such as the one introduced in 1949 by Lars Leksell (1907–1986), a neurosurgeon at the Karolinska Institute in Sweden, work on the principle that a probe whose length is equal to the radius of an arc will reach the center of the arc when introduced perpendicular to a tangent anywhere along the arc. By linear adjustments of the arc support system in three dimensions, the probe is brought to the target. The system is based on the *center-of-arc* principle and the basic components are the Cartesian coordinate frame and a semi-circular arc. The Brown–Roberts–Wells [61] and Cosman–Roberts–Wells [62] are two other arc radius systems.

Polar coordinate systems use a combination of angles and a probe depth measurement to specify a trajectory and a target point. A minimum of two angles in planes perpendicular to each

other plus probe length are required to specify a unique trajectory in 3D space. The Cooper device involves a polar coordinate system that includes calibrated protractors used with a ventriculogram (intraventricular injection of iodine contrast to X-ray identify ventricle landmarks in the brain). A line is marked from entry point to target while the desired trajectory is compared to the actual trajectory and angular corrections are made.

In recent decades, the introduction of brain imaging using 3D computerized tomography (CT) in 1976 and magnetic resonance imaging (MRI) in the 1980s, has significantly improved the ability to accurately identify neuroanatomic targets and thus made DBS a more viable treatment option [63]. Today pre-surgical planning with MRI is common because it allows entry point and trajectory planning and can also be used intraoperatively to monitor targeting accuracy.

Newer imaging systems have been developed with advances in computer technology. One of these is the microTargeting Platform for the microTargeting Drive System [64], a surgical targeting system that attaches directly to a skull-based fiducial marking system. A fiducial marker is an object placed in the field of view of an imaging system that appears in the image produced. The position of this marker in the produced image serves as a point of reference or a measure to enable the alignment of the microTargeting microdrive with a selected target within the cranium. The technology behind a MicroTargeting Platform is based on a patient-specific, computer-generated, virtual, custom mounting interface that allows precise localization of the target, entry point, and a fixed reference.

Although less commonly used for DBS procedures, there are also “frameless” stereotactic systems [65], which provide the surgeon with navigational information, relating the location of instruments in the operative field to preoperative imaging data. The first frameless system was developed by the neurosurgeon David W. Roberts and coworkers in 1986 [66]. Frameless systems minimize invasiveness by more accurately selecting the best trajectory to the target using the stereotactic principle of co-registration of the patient with an imaging study (e.g., the process of transforming several different sets of data, such as superimposition of the patient’s MRI and scans with a brain atlas, into one coordinate system).

DBS NEUROSURGICAL PROCEDURES TODAY

The pioneering work of dedicated physicians, clinicians, and technicians over the last century has led to significant advances in stereotactic and functional neurosurgery. The current therapeutic effectiveness of these neurosurgical procedures depends not only on advanced stereotactic instrumentation and brain imaging devices but also on carefully established inclusionary and exclusionary criteria, consideration of ethical issues, and a team approach to determining potential benefits and risks made on a case-by-case basis [67].

Ethical Considerations

Selection criteria

Careful patient selection is of critical importance in maximizing successful DBS outcomes as it is for other functional neurosurgical approaches for treatment of neurologic and psychiatric disease. Inclusion and exclusion criteria should be established in advance, although each patient must be assessed as an individual. It is standard to include only patients with severe, demonstrable treatment-resistant illnesses. Patients should have the cognitive capacity to understand the potential risks as well as benefits of surgery and to manage their post-surgical stimulator programming and treatment.

Informed consent can be of concern in patients with severe disease and disability who may be desperate for a “cure.” In addition, because electrode implantation is usually conducted while the patient is conscious, it should be recognized that the patient may decide to revoke consent during the surgical procedure, forcing the surgeon to weigh the risk of aborting the procedure against the dictate to do no harm.

It is commonly understood that patients with co-morbidities, such as severe depression or impaired cognitive function should be excluded both because they may not be able to fully appreciate the implications, risks, and benefits of surgery, but also because DBS may exacerbate these impairments. However, DBS as a treatment for severe depression and other psychiatric conditions

presents a challenge to the standard psychiatric exclusionary criteria that were originally developed for movement disorders. Thus, it is imperative that candidacy be addressed on a case-by-case basis using a team approach that draws on the expertise of multiple related disciplines.

The importance of a team approach

DBS is typically performed in institutions large enough to support the team effort required for patient selection, surgery, and follow-up care. For example, at Mayo Clinic we find that patient screening is best accomplished by an interdisciplinary team that includes input from neurosurgery, neurology, nursing, neuropsychology, psychiatry, speech-language pathology, and biomedical ethics. Not only are the assessments of each team member critical to the candidacy decision, but open team pre-decision discussions of the potential benefits and risks on a case-by-case basis allows a forum for concerns to emerge and consensus to be reached. Even when patients are deemed candidates relative to medical, cognitive, and emotional status and social support, ethical issues may remain. Mayo Clinic established their Biomedical Ethics Program in 2013 from which a trained biomedical ethicist can be called upon to independently assess concerns over the patient's understanding, motivations and expectations relative to DBS surgery so as to allow the patient to make a truly autonomous and informed consent. They may recommend the appointment of an independent patient advocate when, for example, a patient feels undue pressure to proceed from family members, a physician, or others on whom the patient feels dependent. This type of team approach is critical not only for routine clinical DBS, but also in experimental studies of new DBS surgical approaches and devices. Only when a clear consensus has been reached among all team members should a patient be considered a DBS candidate.

Surgical Procedure

Although the surgical procedure varies somewhat from institution to institution, all combine modern stereotactic techniques with detailed image guidance. The procedure used at Mayo Clinic

is reviewed here. In the operating suite a Leksell stereotaxic head frame (Elekta, www.elekta.com) is placed on the patient under local anesthesia. The base of the frame is aligned with the orbitomeatal line (a line that passes through the outer canthus of the eye and the center of the external auditory meatus) to parallel the inter-commissural line (a line that connects the anterior commissure to the posterior commissure). The patient is then taken from the operating suite to the MR suite to obtain an MRI with contrast to map the blood vessels and identify the major landmarks, including the anterior commissure, the posterior commissure, and the mid-commissural point. Well-established x , y , and z target coordinates relative to the mid-commissural point are used for planning electrode placement in the predetermined target structure. Commercially available planning software, such as the Compass system, is used to determine the target coordinates and entry point for a safe electrode trajectory that avoids blood vessels and ventricles.

Once imaging is complete and a safe electrode trajectory established, the patient is then returned to the operating room, where, under sterile conditions and local anesthesia, surgery commences. The patient is usually awake in semi-reclined position, and the Leksell head frame is secured to the operating table. Burr holes are placed in the skull at the predetermined entry point. Although microelectrode recording to aid in target location is commonly performed during DBS surgery for movement disorders, the relative usefulness of obtaining extracellular unit activity for other neurological or psychiatric indications remains to be determined. Following placement of the DBS electrodes, test stimulations are conducted using a temporary external stimulator. The patient remains awake so that verbal feedback can be obtained to monitor potential adverse effects. For example, thalamic stimulation may produce paresthesias, indicating current spread into somatosensory thalamus. If such unwanted effects are noted, the electrode may be moved to another location. Confirmation of accurate electrode placement is usually performed first with intraoperative fluoroscopy and then by postoperative MRI or CT. Once the electrode placement is confirmed and trial stimulation deemed successful, a pulse generator is implanted in the chest under the clavicle either during the procedure or several days later. Common stimulation parameters for

neuromodulation of neurological disorders and psychiatric illness include frequencies of 65–185 Hz; amplitudes of 1 to 8 volts; and pulse widths of 60–450 microseconds [68].

DBS requires follow-up adjustment of the stimulation parameters, which is conducted in the outpatient setting by a skilled DBS programmer. Adjustments are made based on patient feedback and objective measures of performance. This process can take several visits and requires the active participation of the patient.

CONCLUSION

We are well beyond the early approaches to targeting brain structures and implanting electrodes for DBS. The effective use of DBS for treatment of certain neurologic diseases is now well established, and its therapeutic scope is extending into the realm of neuropsychiatric conditions and neurocognitive impairments. Technical advances have made possible a vastly superior knowledge of the anatomy and physiology of neurologic and psychiatric symptomatology than was possible in the early twentieth century. New and powerful scientific techniques are now rapidly advancing that understanding still further. Investigations into the mechanisms of DBS and the pathology of neurologic disease have generated more complete understanding of neural interconnectivity and neural network and circuitry function. As the science advances into increasingly individualized treatment and its application extends to a growing list of conditions, it is important that neurologists, neurosurgeons, and psychiatrists are informed of the latest procedures, clinical trials and outcomes, and have access to the best training possible so that we may fully realize the extraordinary potential of neuromodulation for the treatment of neurologic and psychiatric disorders.

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Chapter 2

Biophysical Fundamentals of Neural Excitation

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INTRODUCTION

As described in the previous chapter, deep brain stimulation (DBS) is an important neurostimulation technique for treatment of various neurologic and psychiatric disorders. In the past 20 years, the network mechanisms underlying the clinical effects of DBS have been extensively studied [1–4]. Although these studies have revealed anatomical circuits and pathways associated with pathological behaviors, the underlying mechanisms of action of DBS are not yet completely understood. Application and study of the therapeutic effects of DBS requires a fundamental understanding of the interaction principles between electric fields and the different neural elements (e.g., axons, cell bodies, etc.) affected by such fields [5]. Thus, it is necessary to understand the electrophysiological basis of electrical stimulation and its effects

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on neural tissue [6, 7]. This chapter explores the principles of extracellular stimulation, neural excitability, interactions at electrode-electrolyte tissue interface, and the electrochemical properties that affect the safety and therapeutic benefits of clinical DBS.

EXTRACELLULAR STIMULATION OF NEURAL TISSUE

To appreciate how electrical stimulation can lead to modulation of neural activity, it is paramount that the effects of extracellular stimulation on neural tissue are understood. Experimental and modeling data suggest that axonal and somatic activity of electrically stimulated neurons is decoupled [8, 9]. As current enters and exits the axon in response to extracellular stimulation, both excitation and inhibition can occur at different locations within the cell. In general, cathodic stimuli depolarize the cell membrane in regions proximal to the electrode and hyperpolarize surrounding regions [9]. Anodic stimuli can have the opposite effect. This can result in a paradoxical effect in which the somatic activity can be inhibited, while the synaptic output of the cell is increased [8, 10–12]. It has been suggested that the effects of DBS most likely result from direct activation of axons rather than dendrites or cell bodies [3, 12, 13]. Accordingly, clinical studies have found that the effects DBS of the ventral intermediate thalamus (VIM) and the globus pallidus internus (GPi) are likely mediated through activation of both afferent and efferent axons [14, 15]. It is thus critical that the activation principles underlying axonal activation are understood. The remainder of this section describes the distribution and propagation of extracellular currents throughout neural tissue, the underlying mechanisms of neural excitability, as well as charge transfer mechanisms between electrons and ions at the interface between stimulating electrodes and tissue medium.

Electric Fields in Volume Conductors

Extracellular stimulation involves passing an electrical current through an electrode into a tissue medium. Interactions between

the applied electrical currents and the neural tissue medium generate extracellular potentials that can activate, inhibit, or modulate neuronal firing depending on the magnitude, distribution, and polarity of the extracellular stimuli. Assessing the stimulation effects on neural tissue requires a mathematical description of the resulting electric fields on the surrounding neurons [16].

A volume conductor can be defined as a volume of tissue (e.g., brain tissue surrounding a stimulating electrode) with conductivity (σ) and permittivity (ϵ), in which there is a current source (I). Solving a volume conductor problem (i.e., calculating the potentials generated by neural stimulation) requires finding expressions for the electric field (E) and electric potential (ϕ) everywhere within the region of interest (i.e., volume conductor). The potential field can be characterized by the geometry and conductivity of the volume conductor, as well as by the distance from, orientation to, and intensity of the source current, I . For the purposes of calculating the potentials generated by neural stimulation, neural tissue can be treated as purely resistive [17]. Similarly, the bulk tissue conductivity can be assumed to be linear, such that electric fields generated by different stimulus magnitudes represent scaled versions of the original solution [18].

For a monopolar source, the current distribution is radial and inversely proportional to both the conductivity of the medium and the distance to the source [16]. As such, the current density (J), electric field (E), and potential distribution (ϕ), can be easily calculated in homogeneous (i.e., same conductivity everywhere within the tissue) and isotropic (i.e., conductivity is the same in all directions) medium by

$$E = \frac{I}{4\pi\sigma r^2} \mathbf{u}_r,$$

where $\mathbf{u}$ is the unit radial vector, and r is the distance between the electrode and the measurement point. Similarly, the potential at any point P within the volume conductor located at a distance r from the monopole can be calculated by

$$\phi = \frac{I}{4\pi\sigma r}.$$

Finally, the current density J at any point P can be calculated by

$$J = \frac{I}{4\pi r^2} \mathbf{u}_r.$$

For a dipole source (i.e., the case when two monopolar electrodes are used), the potential at point P can be calculated as follows:

$$\phi = \frac{Id \cos(\theta)}{4\pi \sigma R^2},$$

where $R = \sqrt{r_1^2 + r_2^2}$ and θ is defined as the angle between r and the horizontal line joining the two monopoles, and d is the distance separating both monopoles (Fig. 2.1). It is important to note that the voltage along a line perpendicular to the axis of the dipole at a point equidistant from the electrodes is zero [5]. Therefore, axons passing through this region will not be excited regardless of the stimulus amplitude.

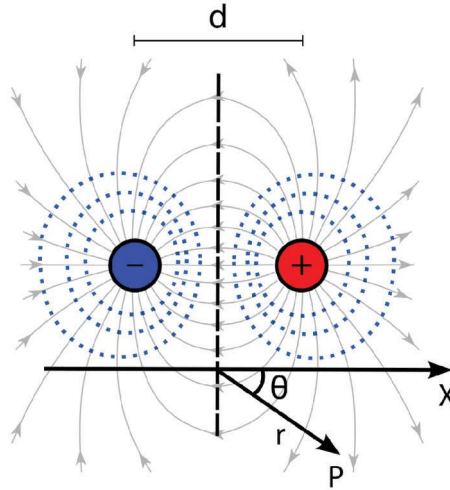


Figure 2.1 Potential generated by bipolar electrode.

For practical applications, however, the electrical properties of neural tissue are inhomogeneous and the tissue is anisotropic.

That is, electrical properties differ relative to their location within the tissue due to multiple factors, such as neural element geometry, orientation, and density [16]. Thus, the voltage at any point P within inhomogeneous and anisotropic mediums can be determined numerically using computer models that rely on the finite element method [19–22].

Neural Excitability

The basis of neuron excitability (i.e., the properties of a neuron that allow it to be activated) lies in the electrical and morphological properties of neurons. As described in the previous section, neural tissue is surrounded by extracellular fluid that can be represented as a volume conductor with a relatively high conductivity of about $80\text{--}300\ \Omega\cdot\text{cm}$ [23]. The tissue conductivity determines how electric fields generated by extracellular stimulation propagate throughout the tissue medium until they reach the neuron. Neurons store electrical energy across a polarizable cellular membrane containing voltage-gated ion channels [24]. In the absence of extracellular stimulation, the voltage across the cellular membrane, also known as the “transmembrane potential”, is maintained by a sodium (Na^+)/potassium (K^+) ATPase, which uses energy from adenosine triphosphate (ATP) dephosphorylation to transport Na^+ out of the cell and K^+ into the cell (1.5 more sodium ions than potassium ions are transported at any given time) [25]. When a supra-threshold extracellular stimulus is applied, the extracellular voltage reaches the gating potential of the voltage-gated sodium channels, and the membrane undergoes depolarization (i.e., excitation). This depolarization leads to a rush of sodium ions into the cell and thus, further depolarization [5, 24, 26, 27]. When the gating potential of voltage gated potassium channels is reached, potassium rushing out of the cell repolarizes the cell, eventually causing a refractory period (hyperpolarization) during which excitation is unlikely (Fig. 2.2). If the stimulus is strong enough to reach the neuron excitation threshold, an action potential will be initiated.

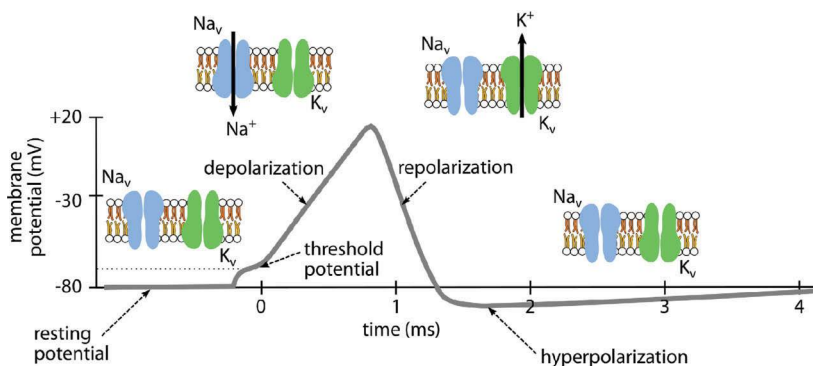


Figure 2.2 Action potential and ionic currents across the neuronal membrane.

Once initiated, an action potential (typically lasting between 0.25 and 5 ms) travels along the axon, eventually reaching the axon terminal, which can be part of a synapse or a neuromuscular junction [28]. Neurons convey information in the form of propagating action potentials travelling along their axon [29]. A discrete sheath of myelin (formed by oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system) insulates most axons, significantly decreasing membrane capacitance and ensuring re-initiation of action potentials in discrete steps at the nodes of Ranvier. In turn, this saltatory conduction, generated by the myelin sheath, increases conduction velocity [30].

Strength-Duration Curve

Neural excitation (i.e., the firing on action potential) is induced by transient flow of electrical currents through the conductive tissue medium [31, 32]. The individual elements of a nerve cell (e.g., soma, dendrites, etc.) have different responses to electrical stimulation. These responses are typically determined on the basis of their rheobase, the minimal current amplitude of infinite duration resulting in an action potential, and their chronaxie, the minimum pulse duration required to achieve an electric current twice the amplitude (i.e., strength) of the rheobase (Fig. 2.3). The current amplitude (I_{th}) required to reach activation threshold and

fire an action potential is inversely proportional to the current pulse width (W), and can be modeled by

$$I_{th} = \frac{I_{rh}}{1 - \exp\left(-\frac{W}{T}\right)},$$

where I_{rh} is the rheobase and T is the time constant of the axon membrane [32–34].

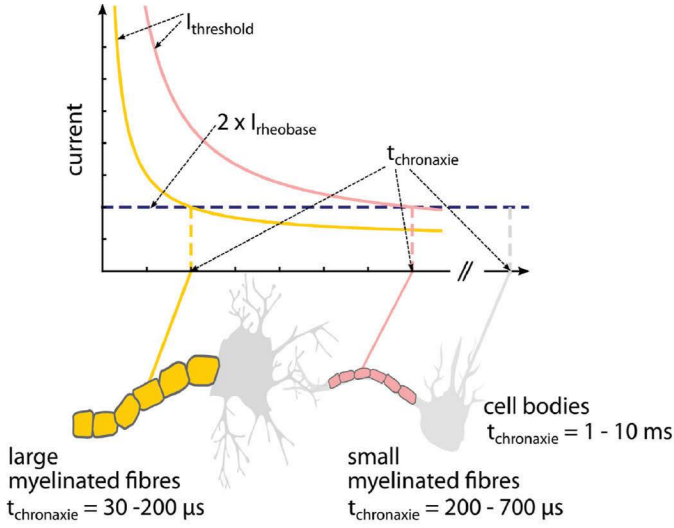


Figure 2.3 Strength-duration curves for large and small myelinated fibers.

However, it is the total injected charge, and not the current amplitude, that dictates the tissue response to extracellular electrical stimulation [35]. The threshold charge injected (Q_{th}) required to activate an axon can be defined as

$$Q_{th} = \frac{I_{rh} W}{1 - \exp\left(-\frac{W}{T}\right)},$$

where the amount of charge required for neural activation Q_{th} increases as the pulse width (W) increases. This results from charge distribution along the axon, which prevents the injected

charge from directly increasing membrane voltage at the excitation site.

Axon Properties

Axon excitation also depends on morphological and geometrical parameters like axon diameter, distance, and orientation from the stimulus source. In synaptic activation, smaller axon fibers are recruited prior to the recruitment of larger axon fibers [36]. However, extracellular stimulation reverses this recruitment order, activating larger fibers followed by smaller fibers with increased current [5]. The amount of current required to activate an axon fiber will increase non-linearly with distance from the electrode [5, 31, 37, 38]. Thus, larger stimulus currents will be required for activation of distant axons [32].

The orientation of the axon fiber with respect to the electric field can also have a significant effect on the neural response to extracellular stimulation [9]. Electrodes placed longitudinally with respect to the axon fibers will generate the most efficient stimulus. Conversely, electrodes placed transversely on each side of the axon (Fig. 2.4) will require higher currents to achieve the same results [5]. That is, the largest component of the field will not contribute to excitation of the nerve. Thus, it is important to remember that it is the longitudinal component of the electric field that is responsible for exciting the nerve [31].

STIMULATION PARADIGMS AND THEIR EFFECTS ON NEURAL ACTIVATION

Electrical stimulation of neural tissue requires that an electrical circuit be established. Such an electrical circuit requires at least one current source and one current sink in the form of anodes and cathodes. Cathodes carry negative potentials and act as current sinks, while anodes carry positive potentials and act as current sources (Fig. 2.4) [39, 40]. Negative extracellular potentials drive the neuronal membrane towards depolarization. In contrast, anodic pulses cause hyperpolarization. Therefore, cathodic pulses are generally used for extracellular stimulation.

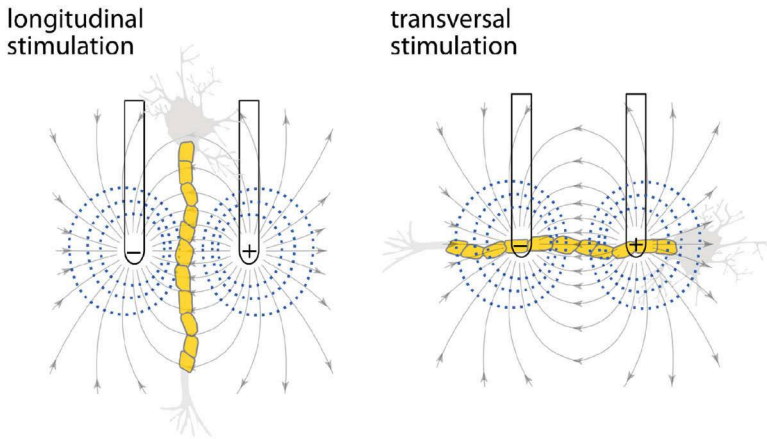


Figure 2.4 Axon fiber orientation and electrical current flow in a bipolar electrode configuration. The figure on the left shows a longitudinal orientation of a myelinated axon with respect to both the anode (+) and the cathode (-). The figure on the right shows a transverse orientation of the same myelinated axon with respect to both electrodes. Dashed contours represent the electric field generated by each electrode. Arrows represent the direction of electrical current flow.

Galvanostatic and Potentiostatic Stimulation

Electrical stimuli can be current-controlled (galvanostatic) or voltage-controlled (potentiostatic). Power consumption can be more efficient with voltage-controlled stimulation because it does not require the large compliance voltage required by current-controlled stimulators. However, the amount of current injected into the tissue will vary and depend upon the impedance of the electrode/tissue interface [21]. In contrast, current-controlled stimulation offers direct control over current injection, regardless of electrode/tissue impedance [41].

Monopolar and Bipolar Stimulation

Both monopolar and bipolar configurations can be used to provide stimulation of nervous tissue [42]. Monopolar electrical stimulation relies on a single stimulating electrode inserted into the neural tissue, and a large area counter electrode located at an

infinite distance from the stimulating electrode [43]. In bipolar stimulation, two stimulating electrodes are inserted into the neural tissue in close proximity to each other, and current flows from one electrode (i.e., current source) to the other (i.e., current sink) [43, 44]. This configuration results in less current spread than in monopolar stimulation, thereby producing smaller, more selective activation areas [45, 46]. Unfortunately, this configuration also results in higher current thresholds, making bipolar stimulation less power efficient than monopolar stimulation [43]. On the other hand, the risk of current spread outside the target region is higher when using monopolar configurations.

Cathodic versus Anodic Stimulation: Anodal Surround Block and Stimulation Efficiency

Depolarization of one region of the neuronal membrane close to the site of stimulation as a result of cathodic stimulation will cause hyperpolarization in regions of the membrane adjacent to the depolarization site (Fig. 2.5). In turn, these adjacent regions will act as virtual anodes [47, 48]. If cathodic stimulation greatly exceeds stimulation thresholds, the virtual anodes will prevent propagation of action potentials via anodal surround block [7]. An opposite effect will occur when anodic stimulation is applied. Membrane hyperpolarization will take place in the region of the axon closest to the stimulating electrode, while adjacent regions will be depolarized and act as virtual cathodes. Anodic stimulation relies on the virtual cathodes to excite axons. Therefore, anodic stimulation is significantly less efficient than cathodic stimulation, requiring higher stimulation intensities. Studies comparing anodic and cathodic stimulation of the feline cortex and dorsal column have shown that cathodic stimulation is four to five times more effective than anodic stimulation [31, 37, 49]. However, neuronal anatomy might be the defining factor in determining the most effective stimulation mode. For example, it has been shown that anodic stimulation on the cortical surface requires lower stimulation intensities due to the dorso-ventral orientation of pyramidal neurons, leading to axonal depolarization and both dendritic and somatic hyperpolarization [50–52].

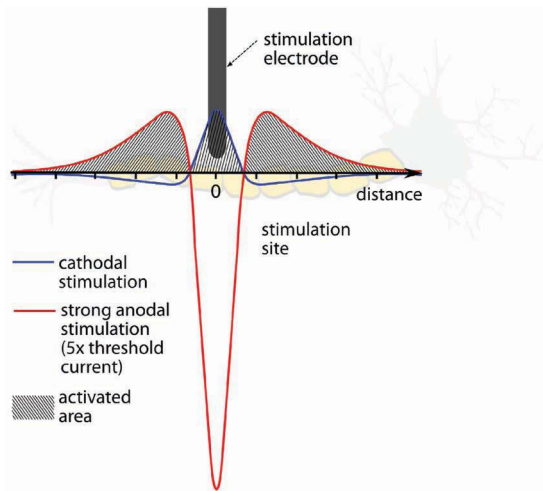


Figure 2.5 Effects of cathodic and anodic stimulation. The stimulating electrode is located at the origin.

Unidirectional Propagation of Action Potentials

Extracellular supra-threshold stimulation of axons produces two action potentials that propagate in opposite directions: orthodromically and antidromically (Fig. 2.6). It is commonly assumed that orthodromic activation will evoke pre-synaptic

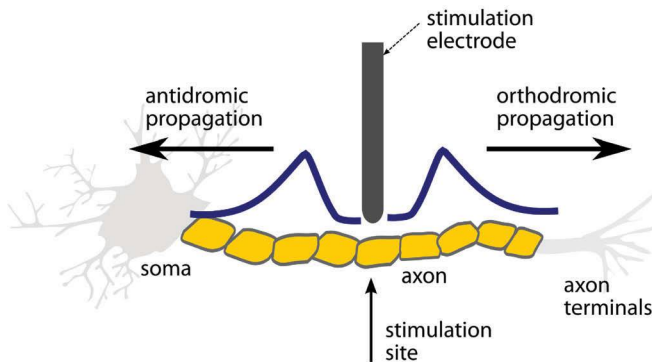


Figure 2.6 A supra-threshold stimulus at an axon leads to creation of action potentials propagating in opposite directions: toward the soma (antidromic) and toward the axon terminals (orthodromic).

effects, while antidromic activation will have no effect on the cell body and dendrites. However, this may not always be true. As such, it is possible to ensure that action potentials propagate only in one direction by using anodic hyperpolarization [53, 54]. Unidirectional propagation is achieved by using an anode to increase the amount of hyperpolarization thereby arresting the depolarizing effects of the propagating action potential generated by the cathode. This allows the action potential traveling in the direction opposite of the anode to escape [55].

Anodic Break

Axonal activation generally takes place at the stimulus onset. However, experimental data have shown that long-duration sub-threshold stimuli (e.g., duration longer than all the involved ionic time constants) can generate action potentials if the hyperpolarization is terminated suddenly [56, 57]. This effect, known as anodic break, has been attributed to the voltage sensitivity of the sodium channel and the time constants of its activation, inactivation, and deactivation states. During the hyperpolarization phase, sodium inactivation increases. When the stimulus ends and the membrane potential is allowed to return to its resting value, the increase in potential causes the sodium activation to increase. However, the sodium inactivation state has a long time constant and remains at an elevated level [27]. As such, the net result during long-duration pulses is an elevated sodium conductance and therefore elevated sodium current, which can reach the excitatory regenerative behavior even at the resting transmembrane voltage. Furthermore, potassium conductance is reduced during hyperpolarization, and recovers only with a time course comparable to that of sodium inactivation. Anodic break can be generated with either cathodic or anodic pulses, since both can hyperpolarize the cell membrane. Avoiding abrupt termination of the current pulse can prevent anodic break. Specifically, stimulus waveforms with slow decay phases (e.g., exponential or trapezoidal decay), have been successfully used to prevent anodic break [58].

Stimulus Waveform

In most clinical DBS applications, rectangular monophasic or biphasic voltage pulses are used to evoke the desired physiological

effects. During monophasic stimulation, either anodic (+) or cathodic (−) pulses are delivered to the neural tissue. Most clinical stimulation devices can deliver monophasic pulses that induce current flow in only one direction (i.e., cathode to anode). The unidirectional current flow associated with monophasic stimulation allows the continued production of faradaic reactions, which ultimately increase the risk of tissue damage [59]. In contrast, biphasic stimulation uses pulses comprised of both anodic and cathodic stimulation phases. Herein, the primary stimulation phase (typically cathodic) is followed by a reversal phase (typically anodic), which delivers current in the opposite direction, thus reversing the electrochemical processes that took place during the stimulation phase and minimizing the accumulation of unrecoverable charge. Conventional DBS paradigms involve a charge-balanced biphasic stimulation waveform that consists of a cathodic stimulation phase followed by an anodic reversal phase.

Historically, stimulus waveforms used in a wide range of animal and human studies have relied on rectangular DBS pulses due to the ease of implementation [60]. However, recent studies suggest that non-rectangular waveforms such as Gaussian, triangular, and exponential decay waveforms offer better alternatives for maximizing axonal activation while minimizing the energy required [35, 61–63]. These optimal waveforms, however, do not guarantee significant clinical differences in the outcomes generated [64].

ELECTRODE/ELECTROLYTE TISSUE INTERFACE

The choice of stimulation paradigm and specific stimulation parameters for activating neural tissue requires a compromise between potentially damaging electrochemical reactions and maximal therapeutic benefits. Therefore, selection of suitable stimulation paradigms should consider the electrochemical properties of the tissue, electrode geometry, neuronal anatomy, and excitability of the tissue stimulated.

Electrode/Tissue Impedance

The impedance of the electrode/tissue interface (Z) represents the resistance encountered by the extracellular current injected at a certain frequency, and is given by

$$Z = R + jX,$$

where R is the resistance and X is the reactance of the equivalent electrical circuit. The magnitude of the impedance is generally determined by the kinetics of the charge transfer processes at the electrode/electrolyte interface and can be modeled using equivalent circuit representations [65] that are beyond the scope of this chapter. For clinical DBS electrodes, impedance can range approximately from 500 to 1500 Ω . From this, Ohm's law ($V = IR$) can generally be used to estimate the potential (V) or current output (I) [21].

Charge Transfer

Charge is carried by electrons in metallic conductors like the stimulating electrode, and by ions in electrolytes like the extracellular fluid [5]. The extracellular fluid in the brain is a complex electrolyte made up of different types of ions such as

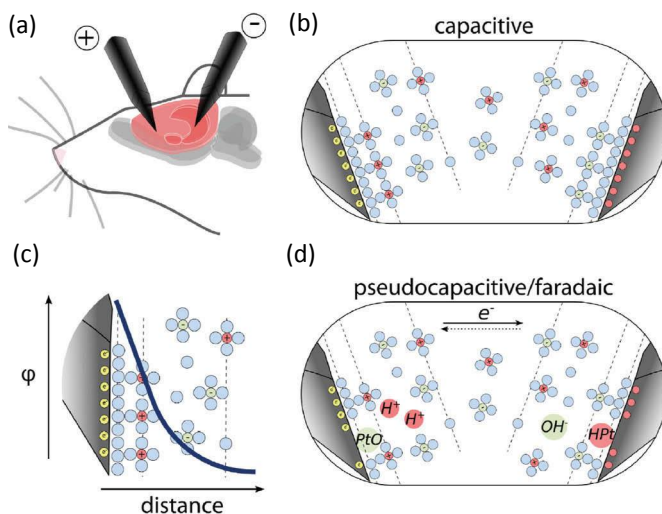


Figure 2.7 Charge transfer at the electrode-electrolyte interface. (a) polarized electrode in a volume conductor (extracellular space); (b) ordered ionic double layer at the polarized electrode surface leading to an exponential decay of the electrode potential; (c) capacitive charge transfer by ionic rearrangements; (d) faradic charge transfer and generation of chemical species bound to the electrode surface (pseudocapacitive).

sodium, potassium and chloride. When an electrical current is applied to the tissue via the stimulating electrode, charge is transferred from electrons in the metal to ions in the electrolyte. During the stimulus pulse, layers of hydrated ions build up on the electrode surface, with a compact ionic layer directly at the electrode surface and diffuse layers at greater distances from the electrode (Fig. 2.7) [66]. When the electrical potential is forced away from equilibrium conditions, pseudocapacitive and faradaic electrochemical reactions may occur at the electrode/electrolyte interface (Fig. 2.7).

Capacitive Reactions

Capacitive (non-faradic) charge transfer is accomplished when the capacitance of the electrode/electrolyte interface is charged or discharged by an electrical potential. This charge transfer leads to ionic rearrangements at the electrode/tissue interface and a flow of ionic currents in the proximity of the electrode [66, 67]. Capacitive charge transfer is preferable because no chemical species are created or consumed. However, capacitive charge transfer alone might not be enough to reach the current amplitudes required for neuronal activation. As such, faradaic charge transfer may occur at the electrode/electrolyte interface in order to reach neuronal activation thresholds [35, 66]. Porous capacitive electrodes or highly dielectric coatings can increase the charge injection capacity of the electrode [67].

Faradaic Reactions

Faradic electrochemical reactions are those in which the electrode surface is oxidized or reduced. These reactions can be reversible or irreversible depending on the relative rates of electron transfer and mass transfer kinetics [66, 68]. Although electron transfer does take place during faradic reactions, chemical species are confined to the electrode surface, and noble metals or noble metal alloys are not consumed (pseudocapacitive reactions) [35].

Irreversible reactions result in the generation of chemical species at the electrode surface that dissolve and diffuse into the tissue, precipitate around the electrode, or evolve into gas before reversal can be achieved [35, 67]. Electrodes operating in the

irreversible region can cause significant tissue damage because irreversible processes can modify the pH of the surrounding tissue and generate toxic products. The most common irreversible faradic reaction is water electrolysis, leading to emergence of H_2 ($2H_2O + 2e^- \rightarrow H_2 + 2OH^-$) at the cathode and O_2 ($2H_2O \rightarrow O_2 + 4H^+ + 4e^-$) at the anode. Additionally, electrode corrosion, which occurs during the anodic phase of stimulation, is a source of major concern because it can cause electrode damage, metal dissolution, and tissue damage [69]. Furthermore, cathodic stimulation is associated with lower activation thresholds than anodic stimulation, thereby minimizing both the injected current requirements and corrosive effects. As such, anodic monophasic stimulation should be avoided, and cathodic stimulation used whenever possible. However, both anodic and cathodic monophasic stimulation can generate irreversible chemical reactions at the interface, driving the electrode into the irreversible region as the current flows in only one direction. For this reason, biphasic charge-balanced stimulation should be used whenever possible.

Tissue Damage

As described in the previous section, tissue damage may result from the products of electrochemical reactions at the electrode-tissue interface. However, these electrochemical reactions are not the only source of stimulation-induced tissue damage. Tissue damage can also occur when excitable tissue is stimulated for extended periods of time. With long-term or chronic stimulation, tissue damage from intrinsic biological processes such as oxygen or glucose depletion and changes in intra- or extra-cellular ion concentrations can occur. For example, excessive firing can lead to increased release of glutamate, causing excitotoxicity by excessive calcium influx [27, 70–72]. This phenomenon is known as the mass-action theory of neuronal damage [35, 73].

Charge Density and Charge Per Phase

Safe chronic electrical stimulation of neural tissue requires not only application of charge-balanced stimulation waveforms, but also analysis of charge density and charge per phase values [71]. The

charge density (in $\mu\text{C}/\text{cm}^2$) is the amount of electric charge Q in a surface or volume:

$$Q = I \times PW / A,$$

where I represents the current intensity, PW the pulse width, and A the electrode surface area. Charge per phase and charge density interact to influence the products of irreversible reactions and determine the threshold of stimulation-induced neural injury. In 1992, Shannon derived an equation that can be used to define the boundary between safe and unsafe charge and charge density levels:

$$\log(CD) = k - \log(Q)$$

where CD represents the charge density (in $\mu\text{C cm}^{-2} \text{ phase}^{-1}$) and Q is the charge (in $\mu\text{C phase}^{-1}$) with the boundary occurring approximately at $k = 1.85$ [65, 74, 75] (Fig. 2.8).

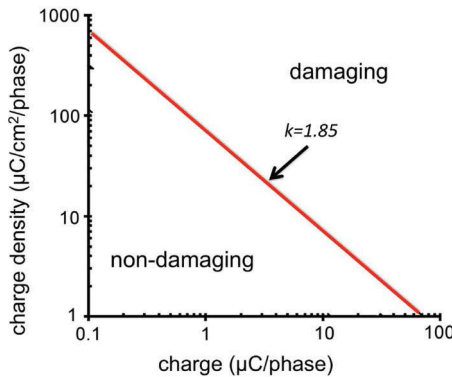


Figure 2.8 Charge density versus charge per phase showing regions of safe and unsafe tissue stimulation. The parameter k defines the boundary between safe (upper right region) stimulation parameters and those that result in tissue damage (bottom left region).

Several studies found that histological damage increases proportionally with charge density at the electrode tip [71, 76]. The safe charge density threshold will vary according to the type of electrode, its metal composition, the stimulation waveform, and the location of the electrode within the body [27, 68, 70–72, 77]. One of the main problems associated with DBS devices in

animal research is the difference in scale. The rat brain is about 1000-times smaller than the human brain, while adult pig brains (~160 g) are comparable in size to that of rhesus monkeys (~100 g) and baboons (~140 g) [78]. Of particular importance to DBS research, the volume of the subthalamic nucleus in the pig ($50 \pm 7 \text{ mm}^3$) is comparable to that of the rhesus monkey ($34 \pm 6 \text{ mm}^3$) [79]. These anatomical differences require a significant reduction of the active surface of the electrode, thereby reducing the maximal current intensity that can be safely applied without producing tissue damage [35]. Early studies with platinum electrodes showed that tissue damage occurred when charge densities between 50 to $300 \mu\text{C cm}^{-2}$ were used [80–82]. Studies using intracortical electrodes can tolerate charge densities up to $1600 \mu\text{C cm}^{-2}$, as long as charge per phase remained below $0.0032 \mu\text{C}$ [27]. More recently, a $50 \mu\text{C cm}^{-2}$ safe charge density limit was reported for platinum electrodes [83]. However, clinically, charge density exceeding $30 \mu\text{C cm}^{-2} \text{ phase}^{-1}$ has shown greatly increased tissue damage risks. For a Medtronic 3387 DBS electrode (Medtronic Inc., St. Paul, MN) with a 0.06 cm^2 contact surface, the current intensity must not exceed 30 mA.

Safety Considerations in Design of Stimulating Electrodes

Clinical DBS electrodes consist of four or more electrode contacts, which might be configured in multiple anode/cathode configurations. These configurations can shape the electric field [84, 85], thus compensating for the heterogeneous conductivity found in brain tissue (i.e., gray matter, white matter, extracellular fluid) and allowing targeting of specific anatomical targets [86]. The use of multiple contacts can also help reduce the risk of tissue damage by increasing the surface area of the stimulating electrode. Existing electrode configurations restrict the selectivity of neural populations that can be activated once a DBS electrode is surgically implanted. As such, there is a need for electrode designs that allow modulation of neural pathways responsible for therapeutic benefits without activating pathways associated with undesired side effects. Spatial targeting, and therefore prevention of side effects, can be improved by using directional electrodes [87].

The risk of tissue damage can be reduced by increasing electrode diameter and height. Furthermore, it has been shown that electrode designs with a low diameter/height ratio maximize the volume of tissue that can be activated, thereby reducing the amount of current required to achieve the same activation effect [88]. However, both electrode height and diameter must follow the anatomical boundaries of smaller brain structures, which can lead to higher charge densities. Finally, electrode material can also play an important role in preventing tissue damage. For example, stainless steel electrodes can induce tissue damage even when following the same design considerations and stimulation parameters as their platinum–iridium counterparts [89].

SUMMARY

As discussed elsewhere in this book, electrical stimulation of neural tissue has been successfully used to treat a wide variety of neurologic and psychiatric disorders. However, continued and safe use of neural stimulation requires an understanding of the underlying effects of extracellular stimulation on neural tissue activation as well as the mechanisms of tissue damage at the electrode/tissue interface. As noted in this chapter, electrode material, geometry, configuration, and stimulation parameters can all have a significant impact on both the therapeutic efficacy and safety of DBS [35, 67, 89]. General safety guidelines include the use of noble metals, such as platinum, for electrode material, as well as biphasic charge-balanced waveforms. These guidelines do not always align with the needs for targeted activation. As such, a compromise is almost always required between optimal acute stimulation effects and safety when applying chronic DBS. It is important to note that there is currently no gold standard for effective, energy efficient and safe stimulation of neuronal tissue, and appropriate conditions have to be determined on an individual basis. Thus, each of the areas covered in this chapter should be carefully considered in designing protocols and devices for existing and emerging treatments that rely on extracellular electrical stimulation of neuronal tissue.

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Chapter 3

Motor Circuit Activity in Parkinson's Disease

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INTRODUCTION

The complex neural circuitry involved in Parkinson's disease (PD) has relevance for a number of neurologic and psychiatric deep brain stimulation (DBS) applications and is thus reviewed in detail in this chapter. PD results from loss of the dopaminergic cells in the substantia nigra pars compacta (SNc). These cells project to the striatum, and striatal dopamine depletion causes the motor symptoms of the disease: bradykinesia, resting tremor and muscle rigidity. Dopamine loss in the striatum and basal ganglia leads to abnormal discharge patterns in the circuitry that controls motor function in the brain, ultimately resulting in abnormal activation of primary cortical motor neurons and concomitant abnormalities of movement. Thus, although the pathologic hallmark of PD is loss of dopaminergic neurons in the SNc, the clinical symptoms of the disease are due to pathologic disturbances in the activity of neurons in the motor control circuits of the brain.

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For this reason, PD, as well as other basal ganglia movement disorders, might properly be considered primarily disorders of neural circuitry. A model for the motor control circuits has been proposed which involves cortico-striatal-pallido-thalamocortical projections. Similar circuitry loops have also been proposed to mediate a variety of non-motor functions and the study of motor circuit activity in PD and movement disorders may therefore serve as a model for the role of circuit activity in behavioral and psychiatric conditions.

THE CORTICO-STRIATAL-PALLIDO-THALAMOCORTICAL MOTOR LOOP

The functional model of basal ganglia circuitry [1–4] provides the anatomical basis for understanding parkinsonian pathophysiology as a disturbance of neural activity in the cortico-striatal-pallido-thalamocortical loops that controls motor function [5]. Early views of basal ganglia function understood it as the convergence and integration of information from diverse areas of the cortex for the control of movement. However, anatomic and physiologic studies from the early and mid-1980s added specificity by identifying the cortical areas that project through the basal ganglia to specific parts of the thalamus and then back to the same cortical area from which the circuit originated. Whereas early views of basal ganglia function were focused on motor control, the current model proposes a family of parallel segregated circuits that mediate both motor and non-motor functions. Five functionally distinct circuits were initially described based on the cortical areas from which they originate, including motor, oculomotor, dorsolateral prefrontal associative, lateral orbitofrontal, and anterior cingulate limbic circuits [1–6].

Because of its importance to movement disorders, the cortico-thalamocortical motor circuit has been extensively studied (Fig. 3.1). Outputs from the motor and premotor cortical areas project to the striatum (putamen). Each cortico-thalamocortical loop is composed of several sub-circuits. The striatal outputs form two functional sub-circuits, an inhibitory (GABAergic) “direct” pathway that projects to the globus pallidus interna (GPI) and the substantia nigra pars reticulata (SNr), and a net excitatory “indirect” pathway that projects to the globus pallidus externa

(GPe) and the subthalamic nucleus (STN). A third sub-circuit, the hyperdirect pathway, makes excitatory projections from the cortex directly to the STN, which then makes excitatory projections to the GPi. The neurons that form these pathways likely receive their input from distinct populations of cortical neurons and the balance and timing of activity between the pathways plays an important role in the proper control of movement.

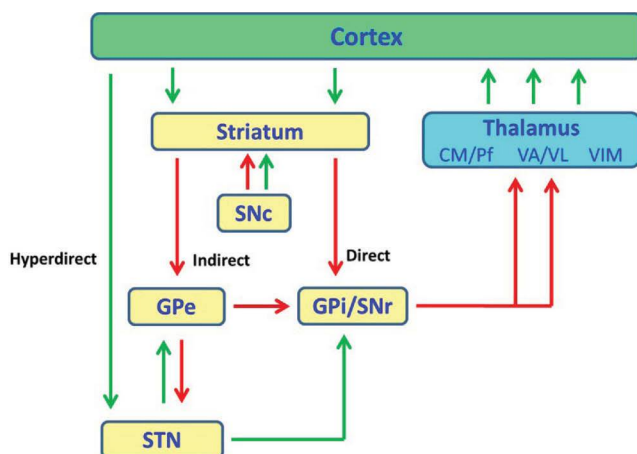


Figure 3.1 Functional anatomy of the cortico-striatal-pallido-thalamocortical motor loop. Projections from the motor cortex form direct, indirect and hyperdirect pathways that modulate motor function. These pathways project through the striatum to the basal ganglia, through the thalamus and then back to the motor cortex. Normal movement is regulated by the balance of activity between these pathways. Red arrows indicate inhibitory connections; Green arrows indicate excitatory connections. SNc, substantia nigra pars compacta; GPe, globus pallidus externa; STN, subthalamic nucleus; GPi, globus pallidus interna; SNr, substantia nigra pars reticulata; CM/Pf, centromedian and parafascicular nuclei of the thalamus; VA, ventral anterior nucleus of the thalamus; VL, ventrolateral nucleus of the thalamus, VIM, ventral intermediate nucleus of the thalamus.

The neurons of the GPi and SNr form GABAergic projections which fire tonically to inhibit specific thalamic nuclei that are involved in motor function (ventral anterior, ventrolateral, centromedian, and parafascicular nuclei). Activation of the striatal neurons that form the direct pathway inhibit the GPi and SNr,

thereby disinhibiting the thalamic nuclei involved in movement and exerting a net excitatory effect. The neurons of the GPe make inhibitory projections to the GPi and the SNr, as well as to the STN. Activation of the striatal neurons that form the indirect pathway inhibit the GPe, thereby disinhibiting the GPi and SNr resulting in increased output and inhibition of the thalamic nuclei.

Nambu et al. [7] have proposed that the direct, indirect and hyperdirect pathways mediate a triphasic center-surround mechanism for the control of movement. At the initiation of voluntary movement, excitatory signals over the hyperdirect pathway activate the GPi (via the STN) which inhibits large areas of the thalamus and cerebral cortex, thereby suppressing the expression of unwanted movements. Signaling through the direct pathway then disinhibits specific targets releasing the motor program for the intended movement. Finally, activity over the indirect pathway may inhibit the motor circuits leading to termination of the motor program. Both the timing and the relative strength of the connections are critical for the proper execution of movement.

MOTOR CIRCUIT ACTIVITY IN PARKINSON'S DISEASE

The balance of activity between the direct and indirect pathways of the cortico-thalamocortical motor circuit is regulated by dopaminergic output from the substantia nigra pars compacta (SNc) to the striatum. Dopamine release from SNc neurons activates the striatal neurons of the direct pathway via D1 dopamine receptors and inhibits the striatal neurons of the indirect pathway via D2 receptors. In PD, neurodegeneration of the SNc with subsequent loss of dopaminergic neurons disrupts the balance of activity between the direct and indirect pathways.

Animals treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA) experience SNc degeneration with the loss of dopaminergic neurons and the development of Parkinson's-like disease. In animal models of PD, changes in the firing patterns of striatal neurons following dopamine depletion have been difficult to document consistently. This difficulty is probably due the heterogeneous nature of this population of cells, although reduced activity in the striatal

cells of the direct pathway with increased activation of the indirect pathway has been reported in 6-OHDA treated rats [8]. In MPTP-treated monkeys, several groups have demonstrated enhanced discharge rates from neurons of the GPi and the STN, with reduced activity in the GPe ([9, 10]; reviewed by [11]). Although the rate of discharge is often reported, changes in the pattern of discharge are also commonly observed, and these may be more relevant from the standpoint of circuit activity and the clinical symptoms of the disease.

Observations such as these from animal models of PD have led to a disease model in which it is thought that loss of dopamine following SNc degeneration leads to inhibition of the striatal neurons of the direct pathway, resulting disinhibition of GPi and SNr. In the indirect pathway, the model proposes that striatal neurons are activated by dopamine depletion, resulting in an increase in inhibitory output to the GPe and leading to further disinhibition of GPi and SNr, as well as the STN. Disinhibition of STN then increases its excitatory input to GPi and SNr, and also to GPe. The overall effect of dopamine depletion is thus an increase in inhibitory output from the GPi and SNr via disinhibition by reduced GPe output as well as increased excitation from STN input, the end result of which is decreased activity in the thalamic and cortical neurons that control movement. This “Rate Hypothesis” model of PD focuses mainly on the levels of activity from these nuclei as determinants of the disease.

Support for the Model

The Rate Hypothesis model of PD is based on circuit dysregulation and is supported by lesion experiments in animals and by the results of therapeutic ablation surgery in humans. If increased activity in the STN and GPi following dopamine depletion are causative for the motor symptoms of PD, it was thought that ablation of these nuclei might alleviate the symptoms. To test this hypothesis several groups performed lesions to the STN in MPTP monkeys. Indeed, such lesions produced significant alleviation of all the major motor disturbances including tremor, akinesia and rigidity [12, 13]. Based on these results, ablation of the STN was tested as a therapy for PD in humans. Called a “thalamotomy,” the procedure of bilateral or

unilateral subthalamotomy frequently produced significantly improved motor scores on the Unified Parkinson's Disease Rating Scale (UPDRS) under both "off" and "on" drug conditions (e.g., drugs, such as levodopa used clinically to counter dopamine loss in patients with PD), [14–17]. Bilateral or unilateral ablation of the posteroventral GPi (pallidotomy) produced similar results relative to the primary motor symptoms of PD [18–20]. However, although unilateral and bilateral ablation of the GPi resulted in significant relief from drug-induced dyskinesias [21], follow-up studies reported a significantly increased incidence of emotional, behavioral and cognitive side effects with bilateral GPi ablation [22, 23].

Reduced activity of the GPe has also been proposed as part of the pathologic mechanism following dopamine depletion. If this is the case, lesioning the GPe might be expected to exacerbate PD symptoms. In MPTP monkeys, ablation of the sensorimotor portion of GPe increased bradykinesia and reduced mobility. In addition, mean neuronal discharge rates from the GPi increased [24].

Although there is some variation in the outcomes and interpretations of ablation studies from both animal models and from human patients, the results have generally supported the basic tenets of the model for circuit dysregulation in response to dopamine loss.

DEEP BRAIN STIMULATION

STN and GPi as Targets for Deep Brain Stimulation to Treat Movement Disorders

In the late 1980s, Benabid and colleagues noted that high-frequency stimulation (100 Hz) applied during clinical stereotactic thalamotomy was able to stop extrapyramidal tremor in the absence of actual thalamotomy [25]. This surprising finding led to the development of deep brain stimulation (DBS) as a treatment for PD. DBS therapy involves local high-frequency stimulation of specific subcortical targets via permanently implanted stimulating electrodes. Electrodes are most often implanted bilaterally in the

brain but unilateral DBS is sometimes used to treat asymmetric symptoms and can have significant bilateral effects. The electrodes are driven by an externally programmable pulse generator implanted in the chest.

The STN and the GPi are the most commonly used and effective targets for the treatment of the motor symptoms of PD. Several studies have shown that especially for patients with advanced PD, DBS combined with medication was more effective than the alternative best medical therapy in improving motor function and general quality of life, while minimizing dyskinesias that are often associated with high dose medications [26, 27]. Studies comparing DBS at the STN and GPi have generally not found significant differences in terms of the anti-tremor effects of the surgery, although these targets may differ somewhat in the quality of their therapeutic effect and in their non-motor adverse effects [28, 29].

The therapeutic mechanisms of DBS are still poorly understood and are likely more complex than those underlying ablation, which involves the simple interruption of abnormal circuit activity. The downstream effects of ablation may be both inhibitory and excitatory and it is clear that electrical stimulation can also inhibit and activate elements of the circuitry at the point of stimulation [30, 31]. However, the effects of DBS go beyond simple inhibition and activation. Electrophysiologic studies following DBS of the STN, GPi and GPe have generally supported the cortico-thalamocortical motor loop model for PD but have countered the Rate Hypothesis in that it is patterns of activity rather than simple rates of discharge that are most important. For example, high-frequency stimulation of the STN in MPTP monkeys increased the discharge rate from cells in the GPi, yet despite these increases the symptoms of the disease were reduced [32]. Of note, the observed discharge rate increase showed a distinct pattern in which action potentials in GPi cells occurred most frequently at 3 and 6 ms following stimulation of the STN. Observations such as these have led to the formulation of the “Pattern Hypothesis” in which changes in bursting and oscillatory activity and in the synchronicity of neuronal activity are considered the critical factors for the development of PD and the effects of DBS, which interrupts and

overrides abnormal basal ganglia outputs to exert its effect [33, 34]. A complete discussion of the proposed mechanisms of DBS can be found in Chapter 16, Theories of DBS Mechanisms.

Functional Imaging Following DBS

Functional imaging studies using positron emission tomography (PET) or blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD-fMRI) to visualize brain activation during DBS have consistently demonstrated activation of elements of the cortico-thalamocortical motor circuit in both animal models and in humans. One recent study reported the first BOLD-fMRI data from patients while they were receiving STN stimulation [35]. The study consisted of ten patients with PD who were studied at least 6 months post-implantation and had responded well to DBS therapy. Patients were off medication at the time of the experiment. Each patient was asked to perform directed hand movements, and imaging was performed in both a stimulation ON and a stimulation OFF condition. In response to DBS, activation changes were observed in the insular cortex and the thalamus. Quantification and modeling of the neuromodulatory effects of the DBS revealed that during voluntary movement, STN stimulation reversed the relative strengths of the cortico-thalamic and the thalamocortical connections.

The previously mentioned study used dynamic causal modeling (DCM) to analyze the BOLD-fMRI response data. This modeling system uses the magnitude and timing of fMRI responses to estimate “effective connectivity” or how the activity of one region causes changes in another, thus allowing the generation of models of the flow of information through circuits and networks. DCM has generally been used to model responses to a particular experimental input such as a voluntary movement, but in a follow-up study, Kahan et al. [36] extended the analysis to allow modeling of the resting state response to STN DBS without the need for an associated input. They found that STN DBS modulates all elements of the cortico-striatal-pallido-thalamocortical motor loop, including the direct, indirect and hyper-direct pathways. STN DBS strengthened connectivity over the direct pathway

which predicted both the clinical severity of disease as well as the therapeutic efficacy of DBS in a given subject. Although stronger connectivity over the hyper-direct pathway appears to be beneficial for PD symptoms, STN DBS reduced the effective connectivity over this pathway. Thus optimal DBS parameters may be those that strengthen the direct pathway while limiting inhibition of the hyper-direct pathway. The activity of the indirect pathway was also modulated, with STN DBS reducing the strength of the connectivity between the striatum and the STN. In general, these results suggest that the efficacy of STN DBS is increased by sensitization of the thalamus to its direct afferents and by desensitizing the STN. The observations from these two studies illustrate that the therapeutic effects of DBS are likely due to changes in the strength of connectivity between elements of the cortico-thalamocortical motor circuit rather than to simple activation or inactivation.

Imaging studies in large animal models have also demonstrated the modulatory effects of DBS on elements of the motor pathway (Fig. 3.2). Min et al. [37] reported that DBS to either the STN or the EN (entopeduncular nucleus; the pig homologue of the human GPi) activated both cortical and subcortical areas of the cortico-thalamocortical motor circuit in the normal anesthetized pig brain. Stimulation of either the STN or the EN/GPi caused BOLD fMRI activation in the ipsilateral sensorimotor areas of the brain, including the primary motor and somatosensory cortex as well as the premotor cortex. The caudate nucleus, anterior cingulate and anterior insular cortex were also activated. Target specific activation was also observed and showed that STN DBS uniquely activated the ipsilateral ventral anterior/posterior thalamus, somatosensory association cortex, prepyriform cortex, hippocampus, lateral geniculate and pedunculo pontine nuclei, the contralateral temporal cortex, parahippocampal gyrus, and cerebellum. EN/GPi DBS uniquely activated periaqueductal gray matter and the superior colliculus. These data support the notion that DBS activates elements of the cortico-thalamocortical motor circuit but also shows that other non-motor areas of the brain can be activated as well. Activation of some of these areas may explain some of the non-motor side effects that can result from DBS therapy.

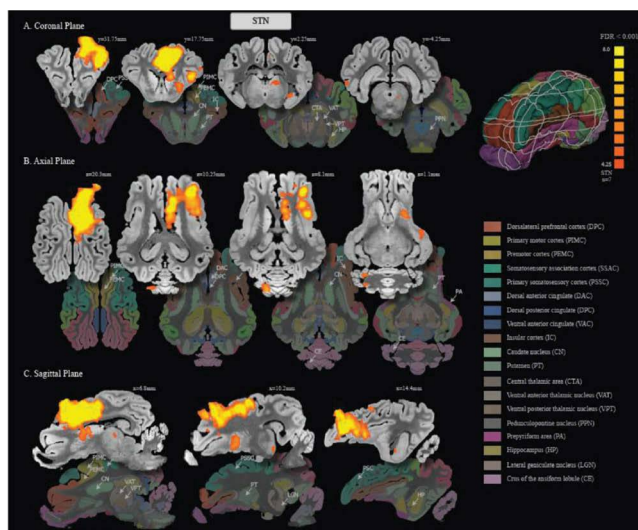


Figure 3.2 BOLD fMRI response of the pig brain following DBS of the STN. Areas of activation with STN stimulation at 1 V 130 Hz 0.5 ms, normalized to a 3D pig brain template. Significant activation ($FDR < 0.001$) was observed in the ipsilateral premotor cortex, primary motor cortex, primary somatosensory cortex, dorsolateral prefrontal cortex, caudate nucleus, putamen, anterior cingulate cortex, insular cortex, thalamus (central, ventral anterior and ventral posterior areas), prepyriform area, hippocampus, lateral geniculate nucleus, pedunculopontine nucleus, and the contralateral cerebellum. Reproduced from [37]. Copyright (2012), with permission from Elsevier.

More recently, imaging studies following STN DBS in non-human primates [38] have demonstrated very similar patterns of activation. The consistency of the patterns of activation that have been observed in pigs, non-human primates, and humans offers validation for the animal models as tools for the study of the mechanisms of action of DBS.

DBS for Other Neurologic and Psychiatric Conditions

The therapeutic success of DBS for movement disorders has led to the application of DBS for an increasing spectrum of neurologic and psychiatric conditions, including obsessive compulsive

disorder, Tourette syndrome, depression, epilepsy, addiction, and intractable pain (see chapters 9, 10, 11, 12 and 13). Although movement disorders and psychiatric conditions may seem quite different, dysfunction of cortico-thalamocortical circuitry is probably central to the pathophysiology of all of these conditions. Five distinct cortico-thalamocortical loops were initially described including motor, oculomotor, dorsolateral prefrontal associative, lateral orbitofrontal, and anterior cingulate limbic circuits [6]. These circuits are similar in the general pattern of the circuitry (see Fig. 3.1) but differ in the cortical areas from which they originate. The thalamocortical motor loop originates from the sensorimotor areas and the postcentral sensory cortical areas, and projects to motor areas of the basal ganglia and thalamus. In contrast, DBS for neuropsychiatric conditions is most often targeted at elements of the prefrontal and orbitofrontal cortices or at the limbic circuits [39]. Dysregulation within and between the thalamocortical loops therefore appears to be the common feature of a variety of neuropathologic conditions and the ability of DBS to disrupt abnormal patterns of activity in these circuits is likely a key component of its therapeutic effect.

SUMMARY

The functional model of basal ganglia circuitry provides an anatomical basis for understanding the therapeutic effects of DBS through the modulation of neural activity in the cortico-striatal-pallido-thalamocortical loops that mediate both motor and non-motor functions. Although the rate of activity over these neural pathways is important, the pattern of activity may also be critical for normal function.

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Chapter 4

Neuroimaging in Deep Brain Stimulation

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INTRODUCTION

As a form of stereotactic functional neurosurgery, the surgical procedure for deep brain stimulation (DBS) relies upon neuroimaging for precise implantation of the DBS electrode. In current practice, surgical targeting is determined primarily by preoperative, image-guided surgical target/trajectory planning, magnetic resonance imaging (MRI) angiography to avoid blood vessels, and by intraoperative electrophysiological confirmation. Following surgery, imaging, usually in the form of computerized tomography (CT), is used to confirm targeting accuracy, which is a major factor in patient outcomes. Today, as imaging science continues to advance, it is also being used to improve our understanding of the central mechanisms of action of DBS.

There is increasing evidence that DBS exerts both its therapeutic and adverse effects by modulating neural activity at the stimulation target site and brain structures that are functionally and anatomically related to it [3–7]. The brain's dense wiring

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has made characterizing the effect of electrical stimulation on neuronal communication beyond a few synapses challenging. However, functional and anatomical neuroimaging appears well suited to this task due to its wide clinical availability and global assessment capabilities. In the clinical setting and in basic and translational research, neuroimaging is helping to improve our understanding of the mechanisms and differential effects of DBS. This chapter reviews several types of clinical neuroimaging relative to their clinical application in DBS and their use as research tools with an emphasis on DBS for Parkinson's disease (PD).

NEUROIMAGING TECHNIQUES

Much progress has been made in the development of computerized medical imaging devices since the first use of CT in the 1970s and of MRI and PET in the 1980s [8–11]. Although we use the term “image,” the images are not photographs, but rather two- or three-dimensional computed images that reconstruct signals emitted by the human body under conditions specific to the type of detection method used. These noninvasive tools are widely applied both in the clinical arena and in neuroscience research for in vivo imaging of the structures and functions of the human brain. To better understand their use in the field of DBS, the basic principles of MRI and PET are explained in simple overviews in the sections that follow. For more detailed explanations on these techniques see *MRI: The Basics* on MRI [12] and *Foundations of Medical Imaging* on PET [13].

Principles of MRI

Magnetic resonance imaging

MRI is based on the magnetic phenomenon discovered in 1946, in which atomic nuclei can absorb and re-emit electromagnetic radiation in a magnetic field [14, 15]. In the magnetic field, protons spin on a rotational axis with a north-south pole, and each atomic nuclei has its own unique spin frequency that is dependent on the strength of the magnetic field, which is called “precession frequency.” Under normal conditions, the rotational axes of protons

are oriented randomly with respect to each other, but when placed in a strong magnetic field they align, creating a second magnetic vector along the axis of the MR scanner. By selecting a certain precession frequency and applying that radio frequency (RF) energy source, one can selectively excite a known nucleus. This is called as a “resonance” phenomenon, and when the nuclei re-emit the absorbed energy, the signal could be detected by the MR scanner.

A medical-use MRI scanner is comprised of three parts: the main magnet, gradient coils, and radio frequency (RF) coils. The main magnet generates a magnetic field around the area of the body to be imaged, and the nuclei, which are aligned with the magnetic field, spin with precession frequency. While the precession frequency of hydrogen protons is of particular interest for medical MRI, a range of other protons can be measured by nuclear magnetic resonance (NMR) spectroscopy.

The gradient coils in the MRI machine are used to alter the strength of the magnetic field in very small, controlled increments which causes the precession frequency of the hydrogen protons to vary linearly along the x , y , and z coordinates. These changes in precession frequency, mapped relative to the dimensional coordinates, are then converted by mathematical algorithms, such as Fourier transformation to form a three-dimensional image.

MRI uses the small differences between two energy states of the hydrogen protons. Some protons align in a direction that is parallel to the main magnetic field of the MRI (low energy state); some spin against the orientation of the magnetic field (high energy state). When the RF coil emits radiofrequencies that match the precession frequency of the “low energy” hydrogen protons, they flip their orientation and become “high energy” protons (known as the “resonance phenomenon”). Protons with the newly acquired “high energy” state will convert back to “low energy” (i.e., re-align with the magnetic field) within milliseconds emitting energy as a waveform. This signal will be measured by the RF coil again, and the signal’s amplitude, that is, the strength of the resonance phenomenon, depends upon the density or hydrogen spin property in the tissue that is being imaged.

When the RF pulses are applied and stopped, two things happen: (1) the synchronicity of precession begins to decay; (2) and the rotational axes of the protons begin to recover their alignment

with the magnetic field of the scanner. The time constants for both decay (T_2 relaxation) and recovery (T_1 relaxation) can be measured, and these rates are dependent upon several factors, including the properties of the tissue in which the protons are located. Varying the RF pulse sequences can produce contrast within these constants, and mathematical algorithms can then be used to generate tissue visualization. During an MR exam, different RF pulse sequences are used to highlight specific tissues and tissue abnormalities depending upon the diagnostic goals. Thus, MR scans can distinguish between white matter, gray matter, the ventricles, and malignant versus normal tissue without the need for exogenous contrast agents. In addition to anatomical or morphological imaging, MRI can also measure blood flow and can produce images of vascular structures using various MR angiography techniques.

The measure of magnetic field strength in MR technology is the Tesla unit, expressed as “T.” One T unit is about 20,000 times stronger than the earth’s magnetic field. Medical-use MRI scanners typically range from 1.5 T to 3.0 T. Compared to the original 1.5 T scanners, 3.0 T systems have greatly enhanced resolution and sensitivity, which has encouraged industry to produce even higher tesla machines that range from 4.0 T to 7.0 T. Although the technology for magnets stronger than 7.0 T exists, their use in humans is hindered by safety concerns. While not used clinically, the 7.0 T MRI scanner is available for research purposes and can produce signals that are four to five times higher resolution than the those obtained from the 1.5 T scanner.

Functional magnetic resonance imaging

It is safe to say that since its introduction in the early 1990s, functional MRI (fMRI), with its ability to produce high-resolution images of patterns of neural activation, has changed modern neuroscience. Functional MRI measures oxygen consumption resulting from neuronal activation, a technique conceived of by Seiji Ogawa and designated “blood-oxygenation level-dependent” (BOLD) MRI contrast [16]. The BOLD signal relies on changes in the ratio of oxyhemoglobin to deoxyhemoglobin, and changes in neural activation lead to alterations in the BOLD signal intensity. This indirect measure of neural firing has made it possible not just to image brain static structures, but to capture dynamic neural

activation and deactivation in response to functional input, be it behavioral or physiologic.

Basic Principles of Positron Emission Tomography

PET imaging uses radiolabeled tracers to image molecular targets of interest. These tracers are compounds and biomolecules containing positron-emitting radionuclides. The tracers are intravenously administered and bind to cell transporters or receptors in targeted tissues.

Positrons are subatomic particles with the same mass as electrons but with a positive rather than a negative charge. Radioactive decay results in the emission of positrons from the tracers at the target tissue. Emitted positrons travel a short distance called the “positron range” before colliding with surrounding free electrons. Positron range can be several millimeters and determines the spatial resolution of PET imaging which is usually 6-8 mm. When a positron collides with an electron, both are annihilated, resulting in the emission of two gamma rays (high energy photons) in exactly opposite directions. The PET scanner consists of an array of gamma ray detectors that encircle the patient’s head and can identify the tracer location by detecting pairs of coincident gamma ray emission signals on opposite sides of the head. The trajectories of many gamma ray emission signal pairs will intersect at points in the tissue that have high tracer concentration and mathematical algorithms are then used to analyze tracer concentration and location, and to reconstruct an image of tracer distribution in the tissue. PET provides various modalities for imaging depending on its radioactive probe targets, such as glucose for energy consumption, neurotransmitters for neurotransmitter receptors, and expressed protein-binding molecules for stem cell tracking.

Related Forms of Neuroimaging

Related forms of functional imaging techniques expand upon common principles of MRI or PET. These include single photon emission tomography (SPECT), a variant of PET, which generates an image that is considered an indicator of neuronal activity. Diffusion tensor imaging (DTI), a variant of MRI, maps the pattern

and degree of diffusion of water molecules and reveals information about white matter function and pathology. Chemical shift imaging, a process of detecting minor hydrogen proton spin differences based on molecular construction, was once thought to be impractical. However, it has been revived in higher field MRI systems, leading to magnetic resonance spectroscopy (MRS), an important method of discriminating and measuring chemical metabolites in tissue.

NEUROIMAGING IN CLINICAL DBS TARGETING

Accurate targeting is considered one of the most critical factors in DBS clinical outcomes. Neurosurgeons use the integration of multiple functional and anatomic reference points to enhance targeting precision, including printed and digitized interactive anatomical brain atlases, MR images, and electrophysiological recordings and databases. Brain atlases show subsections of deep-brain nuclei, like the subthalamic nucleus (STN), that are not well distinguished on 1.5 T and 3.0 T MR images. Despite the fact that it is a single-source atlas, the Schaltenbrand and Wahren's *Atlas for Stereotaxy of the Human Brain* is the most widely used atlas for stereotactic brain surgery [17]. The most common surgical procedure for targeting a brain structure is to co-register the brain atlas to the patient's brain MRI—that is, to combine brain landmarks seen on MRI with the target location pictured in the brain atlas. Unfortunately, this indirect method does not account for individual variation in brain anatomy. For targets like the STN, direct visualization for image guidance would greatly improve targeting accuracy.

As noted in Chapters 3 and 5, the STN is the most common target for DBS in patients with PD. The STN is a small, obliquely oriented, biconvex, lens-shaped mass of gray matter, surrounded by delicate deep-brain structures, that is extremely difficult to visualize with conventional clinical 1.5 T and 3.0 T MRI machines. It typically measures 5.9 mm, 3.7 mm, and 5.0 mm in the anteriorposterior, mediolateral, and dorsoventral dimensions, respectively [18].

Unlike lower tesla versions of MRI, ultra-high-resolution MRI on the order of 7.0 T can identify the boundaries of target areas

like the STN (Fig. 4.1), and as will be seen, the relative positive and negative effects of DBS appear to be related to targeting accuracy *within* STN substructures. The dorsolateral STN is associated with sensorimotor functioning while the anteromedial STN is associated with limbic function. Thus, targeting anteromedial STN may explain some of the adverse cognitive and behavioral effects of DBS for movement disorders [6, 19].

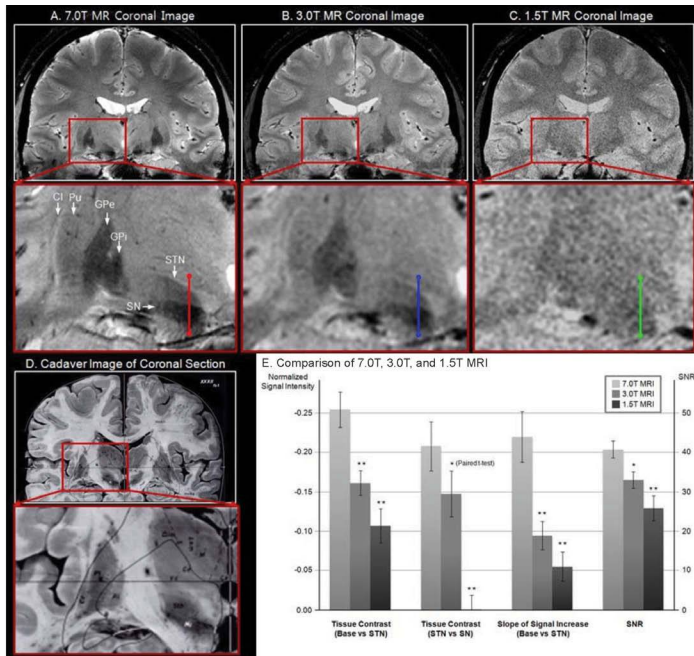


Figure 4.1 Comparison of three Tesla levels of magnetic resonance (MR) images (coronal view). (A) 7.0 T image; (B) 3.0 T image; and (C) 1.5 T image; red boxed off areas of the STN and GPi, target areas important to DBS for Parkinson's disease, magnified below each image. A coronal section (D) from the Schaltenbrand-Wahren brain atlas at the level 3 mm posterior to the midcommissural point (F.p3) is shown as a reference. Graph (E) shows the normalized signal intensity for tissue contrast, the slope of signal increase, and the signal-to-noise ratio. 7.0 T MR was found to perform significantly better across these indices compared to 3.0 T and 1.5 T MR imaging. Abbreviations: DBS, deep brain stimulation; MR, magnetic resonance; GPi, globus pallidus interna; SNR, signal-to-noise ratio; STN, subthalamic nucleus; T, Tesla. Reproduced with permission from [1].

Of note, the STN contains a higher concentration of iron than the surrounding tissues, which causes the anterior part of the STN to have a lower or “hypointense” signal intensity on MRI. The red nucleus, on the other hand, can be visualized on MRI, and its anterior border is easily identified. Thus, using the red nucleus as landmark can assist in targeting the STN.

7.0 T MRI permits direct visualization and thus identification of multiple subcortical structures, including those of the STN, as well as the anterior commissure, mamillary body, red nucleus, cerebral peduncle, substantia nigra, and the surrounding areas. Increased magnetic field strength improves resolution, but also increases the signal-to-noise ratio in a manner that is nearly proportional to field strength, and there is debate about the relative merits of improved image resolution compared with increased signal-to-noise ratio [20] as well as controversy over using MRI alone as a guide for surgical targeting [21–23]. Some of the latter concerns however are based on the capabilities of less powerful MRI machines. Two clinical trials of DBS for PD have found reliable results using 3.0 T MRI for direct targeting [24], and an additional study reported minimal geometric distortion effects with 7.0 T MRI, suggesting the possibility of its future clinical use for the direct visualization of neural structures of interest DBS [1].

FUNCTIONAL IMAGING AS A TOOL FOR UNDERSTANDING DBS MECHANISMS

Although efficacious in carefully selected patients, the therapeutic mechanisms of DBS remain unknown. However, it appears that DBS-evoked alterations in local neural activity at the target site have distal effects. Functional neuroimaging is one of the tools being used to explore both the local and the neural network effects of DBS. These techniques include DTI and SPECT in addition to the more commonly used fMRI and PET. Used in research, these technologies have shown biochemical and anatomical changes within the basal ganglia that contribute to certain movement and affective disorders. For example, SPECT imaging has revealed changes in the caudate and putamen that may help to differentiate early-stage PD from dystonia and essential tremor [25]. PET and

other imaging modalities have shown decreased dopaminergic innervation within the basal ganglia in PD patients [26], and longitudinal fMRI studies have revealed heterogeneity among PD patients, indicating that basal ganglia changes may differ across patients depending upon whether or not they respond to pharmacological therapy [27].

It is understood that STN neurons have an intrinsic pacemaker activity [28] which causes them to fire spontaneously at a frequency of about 20 Hz in the absence of pathology [29]. In PD, they take on a faster, irregular firing pattern with an average frequency of about 40 Hz [30]. Hyperactivity of the STN is thought to reinforce the GABAergic inhibition that the globus pallidus interna (GPi) exerts on the thalamus, leading to hypokinetic motor symptoms [31]. Since lesioning the STN or GPi can reduce Parkinsonism to an extent that is comparable to DBS, DBS was initially thought to exert an inhibitory effect on the STN. Support for this hypothesis was generated from in vivo microelectrode recording studies, which have found decreased somatic firing rates among STN neurons upon application of therapeutic DBS [32–34]. However, studies involving microelectrode recordings of downstream glutamatergic STN projections in the globus pallidus externa (GPe) and GPi support the notion that while DBS may be primarily inhibiting the soma of STN neurons, their axons are functionally excited by stimulation. Stimulation of the STN is thought to result in excitation of target neurons in both orthodromic and antidromic directions [35]. Due to the STN's particularly complex connectivity within and beyond the basal ganglia, a global network approach using functional neuroimaging has become an important means of assessing the effects of DBS.

Many such studies have been aimed at identifying the circuitry that underlies effective versus ineffective stimulation of the STN. For example, a recent DTI study identified a direct relationship between positive DBS outcomes for PD with STN stimulation affecting white matter tracts that are related to the cerebellum [36]. SPECT studies have shown a significant increase in cerebral blood flow in the anterior cingulate/supplementary motor cortex in patients who responded to STN DBS [37] and a correlation between improved motor scores in patients with PD with an increase in regional cerebral blood flow in pre-sensory

motor and primary motor cortex [38]. PET studies have also shown that long-term, effective STN stimulation increases frontal motor/associative area blood flow compared to baseline [39]. These studies suggest that neuroimaging biomarkers may be useful in assessing the effects of DBS for the treatment of PD.

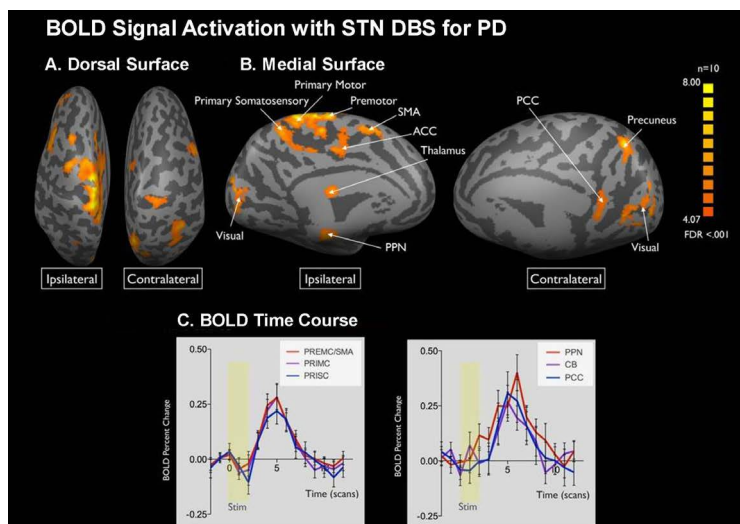


Figure 4.2 Example of cortical areas of significant blood oxygen level dependent (BOLD) activation with STN DBS. Resolved by cortex-based analysis and projected onto inflated representations of the dorsal (A) and medial (B) surfaces of the brain. As seen in both (A) and (B) and the graphs (C), areas of activation included the bilateral supplementary motor area and visual cortex, ipsilateral primary motor and primary and secondary somatosensory cortices, thalamus, anterior cingulate gyrus, pedunclopontine nucleus, and contralateral precuneus (false discovery rate [FDR] <0.001). The mean $\pm$ SD regions of interest were plotted as an average percent change in the BOLD signal over time with each frame lasting 3 seconds and a total of 10 frames (30 seconds) acquired as a baseline measure before initiating stimulation (yellow box). Abbreviations: CB, cerebellum; CC, cingulate cortex; DBS, deep brain stimulation; MC, motor cortex; PCC, posterior cingulate cortex; PD, Parkinson's disease; PPN, pedunclopontine nucleus; SMA, supplementary motor area; SS, somatosensory cortex, STN, subthalamic nucleus. Reproduced from [2].

Functional neuroimaging may also reveal changes in DBS-induced neural activities that underlie adverse effects of stimulation. Indeed, imaging has already identified structural and functional correlates of cognitive and affective deficits associated with PD [40–42] and supports the concept that the site of electrode placement within the STN may have implications for nonmotor circuitry (Fig. 4.2). It has also been suggested that STN DBS carries a greater risk of cognitive and behavioral adverse effects than GPi stimulation [43–45].

The fact that STN DBS can elicit adverse cognitive and emotional effects is not surprising, given our current understanding of the STN as a structure with anatomically-defined subregions that connect not only to motor, but also to associative, and limbic structures [46]. Imaging studies of STN DBS for PD show modulation of both motor and nonmotor areas, including the primary sensorimotor cortex, premotor cortex, supplementary motor area, dorsolateral prefrontal cortex, thalamus, basal ganglia, insular cortex, and contralateral cerebellum [2, 47–52]. PET studies have also implicated the parietal and temporal cortices, classically defined as associative and limbic structures [53, 54].

In a case report in which STN DBS elicited several reproducible episodes of acute depressive dysphoria, fMRI revealed increased BOLD activation in the superior prefrontal cortex, anterior cingulate, anterior thalamus, caudate, and brainstem, with widespread decreases in medial prefrontal cortex activation [51]. Mallet et al. [6] identified STN DBS stimulation parameters and electrode contact areas within the STN that produced a hypomanic state. In a subsequent PET study, they found that anteromedial STN stimulation induced both hypomania and improved motor function which were revealed to be concomitant with activation of limbic and association cortex. A recent clinical report using model-based optimization of STN DBS stimulation parameters to avoid current spread to nonmotor areas demonstrated reduced cognitive and cognitive-motor impairments while maintaining therapeutic motor benefit [7]. Taken together these data suggest that anatomical targeting decisions during human DBS surgery might be augmented by using structural and functional neuroimaging techniques for intraoperative assessment of the motor and nonmotor networks affected by STN DBS.

SUMMARY

Neuroimaging plays a critical role in understanding and elucidating pathological brain function. In DBS surgery it is used as an indirect means of helping to establish target locations. Difficult to visualize targets like the STN, and the fact that subsections of the STN and other targets may generate very different effects, argues for the use of high field strength MRI during pre-surgical planning. Incorporating it into DBS procedures for the direct visualization of such targets would help to advance more individualized DBS treatment.

Functional neuroimaging is also helping to identify DBS-evoked global network activity and proving useful in mapping substructure effects of stimulation parameter settings and DBS contact activation. Thus, through both direct visualization and functional mapping of DBS effects, neuroimaging has the potential to improve treatment outcomes and post-treatment management of DBS PD patients.

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Chapter 5

Ethical Considerations in the Use of Deep Brain Stimulation

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INTRODUCTION

More than a decade has passed since the Food and Drug Administration approved deep brain stimulation (DBS) for neurological movement disorders such as Parkinson's disease (PD) and essential tremor (ET). In the ensuing years, DBS has gained acceptance among neurologists and become an important therapeutic option for patients with movement disorders who are refractory to pharmacological therapy [1–3]. These successes have led to the consideration of DBS for other treatment-resistant neurological disorders, including tardive dyskinesia, epilepsy, certain types of chronic pain syndromes, Tourette's syndrome, and even memory dysfunction [4]. Although the mode of delivering stimulation has remained relatively unchanged since the introduction of modern DBS devices 25 years ago, advances in stimulator programming techniques and parameter patterns, coupled with the identification of novel treatment targets, hold

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the potential to increase the effectiveness of DBS [5] and its applications.

Despite this progress, a number of ethical challenges remain. In particular, it has been difficult to reach consensus regarding the specifics of patient selection. Although clinicians and the multidisciplinary teams assigned to determine individual candidacy of patients agree that cognitive decline and psychiatric factors should be considered, standardized cut-offs for such factors do not currently exist [6]. Additional areas of continued ethical debate and discussion include (among others) age cut-offs for treatment, financial limitations and just access to treatment, and how to address changes in personality that may result from treatment [6–8].

While debates continue regarding the scope of appropriate applications of DBS in neurology, clinicians and researchers have begun to explore the utility of DBS in the context of treatment-refractory illnesses in psychiatry, including obsessive-compulsive disorder (OCD), alcohol addiction, bipolar disorder, and major depression [9–14]. Many of the ethical considerations associated with using DBS to treat these conditions mirror those that were debated prior to its acceptance as a treatment for movement disorders. However, the application of DBS therapy to psychiatric conditions presents a number of additional ethical challenges.

In this chapter, we review ethical considerations in the use of DBS surgery as a treatment for treatment-refractory neurologic and psychiatric conditions. We describe how the use of DBS introduces ethical complexities related to patient evaluation, informed consent, and postsurgical management and discuss strategies for managing these and other DBS related ethical complexities.

ETHICAL CONSIDERATIONS IN DEEP BRAIN STIMULATION

Deep brain stimulation was approved as a treatment for ET in 1997 and for PD in 2002 [7]. Given the inherent risks of neurosurgery and implantation of electrodes in the brain, the treatment is not without risk. In addition to the physical risks of the procedure itself—which include bleeding, infection, and in rare cases, death—these risks include cognitive, behavioral, and emotional adverse effects [15]. DBS therapy also entails substantial

financial costs and an intensive postoperative care regimen. These burdens may be exacerbated for some patients, including patients with limited financial resources or those who must travel some distance to work with a DBS specialist.

Many of the ethical issues associated with DBS have been described by others and include challenges related to patient selection, patient autonomy and informed consent, and postsurgical care [7, 8, 15–17]. These issues are likely to persist and to manifest in even more challenging ways as DBS is used in less conventional neurologic and psychiatric applications.

Patient Selection

Deciding which patients should receive DBS often involves balancing multiple ethical priorities, including ethical commitments related to beneficence, non-maleficence, and justice. Inclusion and exclusion criteria must be established to determine which patients are most likely to benefit most from the intervention. This entails selecting patients who have severe, treatment-resistant illness and the physical, cognitive, and emotional resources to tolerate both the surgery and postsurgical treatment regimen, which includes understanding and participating in programming the parameters of stimulation amplitude and frequency (Hz) [7, 8]. Patients also must be able to manage the psychosocial burdens of surgery and follow-up care [6].

The nature of psychiatric illnesses makes patient selection for DBS more challenging than for other patient populations. The exclusion criteria for DBS in movement disorders typically include the presence of psychiatric comorbidities. Applying similar standards to psychiatric patients becomes inherently more difficult because the disorder being targeted is itself psychiatric in nature, and many psychiatric illnesses present with additional psychiatric comorbidities [18, 19]. In the context of selecting patients who are most likely to benefit from DBS surgery, the issue of comorbidities presents a selection paradox. On the one hand, it is essential to select the sickest patients for whom all other treatment options have failed. However, these are the very patients who are likely to have multiple psychiatric comorbidities, making it difficult to assess the potential benefits of treatment [18].

The extensive postsurgical follow-up required with DBS makes it imperative that patients also have adequate emotional resources and social support. This can be challenging for all patients, but is an area in which psychiatric patients may be especially vulnerable. Patients with obsessive compulsive disorder (OCD), for example, tend to exhibit lower social and emotional quality of life, especially patients who fail to respond to conventional treatments [20]. Social isolation is also common among patients with severe psychiatric illnesses such as major depressive disorder (MDD) [21].

Current approaches for determining DBS eligibility seek to protect patients by ensuring that candidates have exhausted all other treatment options and have the personal resources necessary to do well following implantation. Following these criteria may result in denying the most vulnerable patients access to unproven, but potentially beneficial treatments such as DBS. Requiring that patients have exhausted all other treatment options may limit patient eligibility to those who have the financial and social resources to pursue those more conventional treatments. Combined with the costs of DBS surgery and postsurgical care, which have been estimated to be upwards of \$80,000 per patient [22], the financial burden of DBS can be substantial. Questions about the proper allocation of medical resources will continue to be debated in the context of this financial burden.

Use of DBS for psychiatric conditions is still experimental, and relatively few randomized control trials have been completed. The recent FDA approval of DBS for OCD under a Humanitarian Device Exemption (HDE) is intended for a condition that affects less than 4,000 individuals per year in the United States (21CFR814.100 [2014]). This has generated some controversy due to the possibility that the proportion of eligible candidates may be too high to warrant such an exemption [23]. The FDA has rejected that criticism, and a recent analysis by Garnaat and colleagues confirmed that a very small proportion of OCD patients (less than 1%) will meet criteria for neurosurgery [24]. Although it is unlikely that DBS is being over-used under a HDE, this debate highlights the reality that new and experimental applications of DBS may blur traditional boundaries between patient care and clinical research.

Patient Autonomy and Informed Consent

With any high-risk treatment involving patients with severe illness and disability, the promotion of patient autonomy is a concern. Such individuals may feel desperate and be quick to agree to potential treatments without a thorough evaluation of their risks. This is an especially difficult ethical challenge in the context of severely debilitating, treatment refractory disease but by itself does not imply that patients considering DBS are unable to volunteer for studies and give informed consent to the procedure [8]. However, considering the novelty of applying DBS to psychiatric illnesses and the variability in DBS response rates (~40–60% for refractory OCD and MDD depending on the stimulation target), setting appropriate expectations regarding potential benefits of treatment is especially important for these patients [9].

The nature of the implantation procedure for DBS presents additional challenges related to respecting patient autonomy. Because many patients are awake during the implantation surgery, it is possible that they may revoke their consent midway through the procedure. Depending on the risks associated with aborting the procedure, a neurosurgeon may face the difficult decision of weighing a patient's autonomy against his or her own duties not to cause harm [15]. Additionally, because cognitive impairments can be an unintended side effect of DBS surgery, a patient's decisional capacity may be compromised as a result of the procedure, further complicating decisions about whether to respect a patient's revocation of consent to surgery or subsequent requests for explanation.

Many neurologic and psychiatric illnesses are associated with psychological or cognitive impairments, which further complicate efforts to promote patient autonomy and establish appropriate expectations about DBS. There is some debate around the extent to which such impairments may diminish patients' ability to fully appreciate and weigh the potential benefits and risks of DBS. In the case of psychiatric patients who are not psychotic, many clinicians and researchers have concluded that these impairments can be managed and that autonomous patient decision making can be facilitated through intensive educational efforts [16, 25–28]. Others have argued that certain manifestations of neurologic or

psychiatric disease can alter reasoning, information processing, and memory in ways that cannot be mitigated and can make authentic patient consent impossible [29, 30]. These debates highlight the importance of thoroughly evaluating decisional and cognitive capacity in each individual circumstance, regardless of the disorder type. For example, when patients have suicidal ideation or may not view death as a negative outcome of treatment [30], teams should consider whether these beliefs create decisional impairments that are significant enough to suggest that the patient cannot provide informed consent to DBS surgery.

Although severe neurologic or psychiatric illness can be associated with diminished capacity to participate in medical decisions, each circumstance is unique, and each patient's understanding of potential benefits and risks must be assessed on a case-by-case basis. In cases where the use of DBS is still considered experimental and is provided under a research protocol, therapeutic misconception should also be evaluated [27]. Having decisional capacity does not preclude holding unrealistic hopes and expectations for treatment results that are substantially inconsistent with the expectations communicated by the medical team [30]. These considerations further highlight the importance of discussing the potential benefits, risks, and likely outcomes of DBS throughout all stages of treatment.

Postsurgical Follow-Up

Despite effective symptom reduction in certain DBS applications, determining an adequate metric for “successful” treatment can be difficult. Although many patients with PD report improvements in motor functioning and quality of life following DBS, others indicate that they did not benefit from DBS in their *subjective* evaluation [31, 32]. This in turn may lead to a situation in which “the doctor is satisfied, the patient less so” [31]. Unrealistically high expectations may play a significant role in this dynamic, underlying the importance of a robust informed consent and presurgical education process. Difficulties in adjustment to life following stimulation, changes in self-perception, and familial problems may also play a role [15] in subjective dissatisfaction.

Psychiatric patients face additional postimplantation issues that may require special attention. While reduction in symptoms can occur quickly (within hours or days) following the initiation of chronic stimulation for patients with movement disorders or pain, for example, it may take months to achieve results for psychiatric conditions such as MDD [28, 33]. This delayed response complicates the stimulator programming calibration process, and may make it difficult to determine if changes are having a positive or negative effect [28].

Even when patients respond positively to DBS, there may still be long-term follow-up issues. For example, even in the most successful DBS treatments, total remission of symptoms may not be a realistic outcome. In cases of DBS therapy for MDD, it is also important to emphasize that the goal of extended euphoria (which may be experienced during surgery) is as unrealistic as is the complete absence of depressed mood. Patients can and will become sad when appropriate, which may be troubling to those who dread the return of depressive symptoms [28].

The Issue of DBS-Related Cognitive Alterations

Several lines of evidence suggest that DBS targeting the subthalamic nucleus (STN) in patients with PD may be associated with cognitive decline in certain domains such as verbal fluency, verbal memory [34] and executive function [35]. On the other hand, targeting other brain regions such as the fornix, nucleus basalis of Meynert, or the lateral hypothalamus have shown promise in enhancing certain domains of cognition in preclinical models [36, 37]. This specific issue of DBS-induced cognitive enhancement raises several important ethical issues. The benefits of enhancing cognition in patients with primary cognitive disorders such as Alzheimer's disease or other dementias is substantial to patients, their families, and society at large. Furthermore, improving cognitive function in patients with disorders such as traumatic brain injury, schizophrenia, or severe depression may lead to better quality of life and reduce societal burden. As noted in Chapter 14, DBS is under early investigation as a treatment for episodic memory loss associated with Alzheimer's disease and Parkinson's disease dementia.

If indeed DBS can enhance certain areas of cognition, the issue of normal individuals seeking treatment introduces new layers of ethical complexity. It is well known that certain healthy individuals take medications such as modafinil or methylphenidate to improve academic performance [38]. Although less likely, the pursuit of DBS by healthy individuals to enhance cognitive performance could become a similar phenomenon. The discussion of these possibilities should be ahead of science because reconciling these hypothetical possibilities with ethical principles and societal norms will require extensive debate and discussion among ethicists, scientists, and patient communities.

MANAGING ETHICAL CHALLENGES IN INVESTIGATIONAL APPLICATIONS OF DBS

Little consensus exists regarding best practices for managing ethical challenges associated with applications of DBS in psychiatry. This is not surprising given the early status of such applications. Nonetheless, the experience of several of the clinical teams who have pioneered this work suggest a number of practical steps that may be useful in identifying and managing the ethical challenges outlined above. These recommendations are summarized in Table 5.1.

Given the diversity of clinical perspectives that are relevant to assessing whether patients are or are not good DBS candidates, it is useful to establish multidisciplinary review teams to determine patient eligibility. These teams often include specialists in psychiatry, neurology, neurosurgery, behavioral psychology, psychometrics, nursing, social work, speech pathology, and bioethics. One advantage of convening regular multidisciplinary patient selection reviews and postsurgical debriefing sessions to review outcomes is that it provides team members a forum for discussing potential ethical, medical, or other patient care concerns that they may have. Candid discussion of these matters helps facilitate the identification of emerging areas of consensus. At Mayo Clinic, we have adopted this approach and have found it useful as a way to encourage dialogue across relevant areas of expertise, thereby improving patient care.

Table 5.1 Recommendations for managing ethical considerations in the use of DBS for treatment refractory psychiatric conditions

Ethical consideration	Recommendation
Patient selection	• Exclude patients that exhibit impaired reality upon testing • Develop screening tools to increase quality of referrals • Incorporate multidisciplinary teams to assess patient eligibility
Patient autonomy and informed consent	• Assessment of decisional capacity and/or competence • Evaluate impact of mental illness on family and caregivers prior to consent • Evaluate evidence of therapeutic misconceptions
Postsurgical follow-up	• Provide psychological counseling and social services to patients and monitor psychiatric and psychosocial side effects • Provide long-term support and consider telehealth options for patients living in remote areas • Incorporate DBS treatment into advanced directives • Create clinical databases and national consortia to track long-term outcomes and experiences with DBS treatment

Source: Based on [6, 8, 30].

Another practical step that can be taken to promote the development of consensus standards in the area of ethics and DBS is to establish a national database of outcomes associated with DBS as a treatment for given disorders. As noted earlier, DBS for psychiatric and certain neurologic disorders is provided under a research protocol or an FDA-approved humanitarian device exemption. As a result, the clinical circumstances associated with its use vary widely. This makes systematic data collection and comparisons across clinical sites difficult. To address this challenge, it may be useful to establish a national consortium of

interested clinicians, who can review presurgical procedures, clinical techniques, and outcomes as a first step toward the creation of a national registry of patient outcomes following the use of DBS. By fostering discussions across clinical programs, such a consortium might also facilitate the development of standardized presurgical review procedures or eligibility criteria for the receipt of DBS as an experimental intervention.

To address some of the ethical challenges associated with obtaining meaningful patient consent to the use of DBS, clinical teams might also consider establishing a patient advocate or consent facilitator who works closely with the team to promote autonomous decision making. At Mayo Clinic, we have specialists in biomedical ethics meet with patients independently to assess factors that might impair the patient's ability to provide informed consent. During this interaction, the ethics specialist explores the patient's motivations for pursuing DBS surgery and personal expectations for benefit following surgery in order to provide the team with another source of information to assess whether the patient's expectations are realistic and appropriate.

The ethics specialist also explores the extent to which the patient may be feeling pressured by others to pursue DBS. Such pressures may come from family members or friends upon whom the patient may be highly reliant. It is also possible that such pressures may be the result of long-term clinical relationships. An ethics specialist can explore whether patients are feeling a sense of obligation to pursue DBS or other new treatments in response to a recommendation made by their primary physician or another member of their care team. Although this approach has its limitations, it is an additional step that may enhance autonomous decision making.

CONCLUSION

Understanding of the human brain continues to grow at an exponential rate. These advances will continue to spur new applications of DBS as an experimental intervention for treatment-refractory neurologic and psychiatric conditions. As the field moves forward in the many ways that are foreshadowed in the

chapters that follow, it is imperative that the ethical challenges introduced by these advances continue to be thoughtfully engaged by clinicians, patients, and society at large.

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PART II
CLINICAL APPLICATIONS



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Chapter 6

Deep Brain Stimulation for Parkinson's Disease

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INTRODUCTION: CLINICAL FEATURES AND PATHOPHYSIOLOGY

In 1817, British physician James Parkinson published a manuscript describing what he termed the “shaking palsy” [1]. This treatise was based on his observation of six cases, some of whom were seen as patients and some whom were casually observed in the street. Dr. Parkinson's was the first well-formulated description of the four cardinal features of what has come to be known as Parkinson disease (PD): resting tremor, bradykinesia, rigidity, and gait disturbance. The resting tremor of PD tends to improve when a patient holds out his or her arms or during active movement and tends to worsen during mental distraction. Parkinsonian bradykinesia refers not only to the slowness of movement but also to a decrement in amplitude of movement. It is often assessed by having a patient attempt to rapidly tap

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fingers or open and close the hand. Rigidity is an increase in tone during passive movement and usually includes a ratchet-like “cogwheeling.” Gait disturbance includes both bradykinetic components, such as a stooped posture, shuffling steps with shortened stride length, and reduced arm swing, as well as a postural instability component, which may lead to falls.

By the 1920s, neuropathological studies revealed that degeneration of the pigmented neurons within the substantia nigra pars compacta was a hallmark of disease [2]; however, it was not until 1960 that striatal dopamine depletion was definitively demonstrated in PD [3]. This discovery soon led to attempts at dopamine replacement, beginning with administration of levodopa, the biochemical precursor to dopamine [4]. Dramatic improvements in motor parkinsonism were seen, and in 1969 a double-blind placebo controlled trial was published establishing levodopa as a highly effective therapy in PD [5].

The initial excitement over the discovery of levodopa's effects was somewhat tempered by the later realization that, with advancing PD, other motor complications often develop [6]. These include motor fluctuations, most often experienced as a wearing-off of the levodopa effect between doses. In severe cases, patients may need to take levodopa at intervals as short as every 90 minutes to maintain consistent motor effects. In addition to experiencing fluctuations, patients on levodopa may develop drug-induced dyskinesias which are choreiform “squirmy” movements of the face, neck, trunk, or limbs. Dyskinesias usually occur at the time of peak levodopa serum levels, about 20–40 minutes after oral administration. Patients with both motor fluctuations and dyskinesias often cycle between each dose, “yo-yoing” between a medication-OFF state with poor movement, a dyskinetic state with excessive movement, and a well-treated state.

In an attempt to address motor complications, additional classes of medication, such as catechol-O-methyl transferase inhibitors, monoamine oxidase type B inhibitors, and dopamine agonists have been introduced [7]. While these may be somewhat helpful, as PD advances patients' fluctuations and dyskinesia may not be adequately addressed with medical therapy alone. However, it is important to realize that even in advanced PD, levodopa is still very effective during the so-called medication-ON time.

TREATMENT WITH DEEP BRAIN STIMULATION

Historical Background

Even before the discovery of levodopa, surgical treatments for PD were being explored. Early attempts focused on lesioning along the corticospinal (pyramidal) tract. This led to improvement in tremor and rigidity but at the expense of upper motor neuron weakness and spasticity. As more became known about the importance of the modulatory (extrapyramidal) system of the basal ganglia to motor programming and execution, attention turned from the pyramidal to extrapyramidal system, and thalamotomy and pallidotomy were found to improve parkinsonian symptoms without the adverse effects of pyramidal tract lesioning. Low-frequency intraoperative test stimulation was generally used prior to the actual ablation surgery in order to screen for adverse effects that may occur with a lesion in the thalamus or globus pallidus. In the 1980s, it was discovered that high-frequency electrical stimulation of these regions was often as effective in controlling symptoms as lesioning itself [8]. Due to the relatively reversible nature of DBS, as well as the ability to easily increase the region of affected tissue through programming the stimulation levels, DBS soon overshadowed lesioning procedures as the favored surgical treatment for PD.

Indications

In PD, DBS generally improves those symptoms that respond well to dopaminergic medications such as levodopa. These include the resting tremor, rigidity, upper extremity bradykinesia, and the bradykinetic component of gait (in that order). The overall effect is to attenuate the severity of the medication-OFF state. Because the difference between the ON and OFF states is narrowed, motor fluctuations can be smoothed out. Dyskinesias improve by virtue of both the medication reduction that is usually possible after DBS and likely by a direct anti-dyskinetic effect of DBS. An exception to the general rule that DBS only treats levodopa-responsive symptoms is tremor, which almost universally improves after DBS regardless of its response to medications.

Because DBS has a mechanism of action that is complementary to that of medications, it can also be considered in patients who are unable to take medication because of adverse effects, such as extreme nausea, fatigue, or behavioral changes.

Indications for DBS in Parkinson Disease

- (1) motor fluctuation
- (2) dyskinesia
- (3) medication-refractory tremor
- (4) medication intolerance

Symptoms Poorly Addressed with DBS

In general, symptoms that are not well treated with medication are also not well treated with DBS. These include speech dysfunction, gait freezing (particularly when it is refractory to medication), imbalance with or without falls, and the myriad of non-motor symptoms of PD. The latter include autonomic failure which may manifest as constipation, orthostatic hypotension and lightheadedness, urinary urgency or incontinence, and impotence. PD-related mild cognitive impairment or frank dementia are common and are not addressed by DBS. Mood disturbances including depression, and even more often anxiety, are not directly treated by DBS.

Therefore, while DBS can be a life-changing therapy in a properly selected patient, care must be taken to set appropriate expectations from the start; even if DBS-refractory symptoms are not present at the time of surgery, they will likely develop at some point in the course of the disease, and often will become the primary source of disability in late-stage PD.

The “Ideal Candidate”

A profile for the ideal candidate for PD DBS can be constructed from the above two sections. The ideal candidate would have an excellent levodopa response that is interrupted by problematic motor fluctuation and dyskinesia. He or she would have no medication-refractory gait symptoms, mood disorder or cognitive decline. Excellent overall health would reduce the chances of complications of surgery. Timing is important. If surgery is

performed too early in the course of disease when patients are able to manage with medications alone, then patients will be exposed to unnecessary risks of surgery. However, if patients wait till the later stages of PD when non-treatable symptoms predominate, then they will have missed the so-called “window of opportunity” to maximally benefit from DBS.

DBS TARGETS AND OUTCOMES

Standard DBS targets in PD include the subthalamic nucleus (STN), globus pallidus pars interna (Gpi), and the ventralis intermedius (Vim) nucleus of the thalamus. Stimulation of either the STN or Gpi can improve all four cardinal symptoms of PD, whereas stimulation of the Vim generally improves only tremor and is therefore used in a limited subset of PD patients. While the near-immediate and sometimes dramatic improvements seen after DBS of these targets gave momentum to early DBS efforts, formal quantification of its benefits and comparison to other treatment modalities has been longer in coming.

Any attempt to quantify the benefits of DBS depends on defining measurable outcomes. Standard PD outcome measures originally defined for drug trials were later applied to DBS studies. The Unified Parkinson Disease Rating Scale (UPDRS) quantifies several aspects of PD; part III of this scale involves a systematic motor examination and serves as a measure of the severity of motor parkinsonism at the time of scoring. The UPDRS part III score increases with increasing levels of impairment. In a patient with fluctuations, the UPDRS-III would be expected to change throughout the day so it is usually administered during either the medication-on or medication-off state.

While the UPDRS-III motor exam quantifies the severity of the OFF state itself, the degree of fluctuation throughout the day is better assessed through the use of motor diaries. Typically, a patient is asked to keep a diary for three consecutive days marking each 30 minute period of time as time spent asleep, in the medication-on state without dyskinesia, in the medication-on state with troublesome dyskinesia, and in the medication-off state. An analysis of the data can show during what proportion of the waking day a patient is in a desirable versus undesirable motor state.

The Parkinson Disease Questionnaire-39 (PDQ-39) is a self-administered questionnaire addressing eight domains of functioning and well-being (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort). The PDQ-39 has become the standard by which quality of life in PD is assessed and, as such, has frequently been used as an outcome measure in both drug and DBS trials.

In the early era of DBS, prior to 2006, evidence for efficacy was based on smaller, often uncontrolled and open-label series. Those series with at least 10 subjects and 6 months of follow-up were reviewed in a 2006 meta-analysis [9]. The 37 cohorts included for review were comprised of 921 total patients with a mean age at surgery of 59 years and an average duration of PD prior to surgery of 14 years. Overall, the UPDRS-III motor scores in the medication-off state improved by 52% (95% CI = 48.1 to 56.5%) after DBS. Dyskinesia were reduced by 69% on average. Analysis of motor diaries demonstrated an average decrease in the duration of medication-off time by 68%. Adverse events directly related to the procedure were experienced by 11% of patients.

While this meta-analysis helped to strengthen the evidence base supporting DBS in PD, it also highlighted the need for larger randomized controlled trials. There are multiple challenges in designing and conducting such trials, including the high cost of surgery and devices, the difficulty in blinding patients and examiners to surgical and stimulation status, and the ethical concerns about asking control subjects to wait for an extended period of time after an invasive procedure before the device is turned on. Despite these challenges, over the last decade several large, well-conducted trials have been completed. They are reviewed below.

Deuschl et al. (2006) Trial

The first of these studies compared STN DBS with medical management alone in 156 European PD patients with disease duration of at least 5 years who were insufficiently treated with medications [10]. After pair-wise randomization to STN DBS or best medical management, patients were followed unblinded for 6 months. The DBS patients experienced significant improvement

in quality of life according to the PDQ-39 scale, whereas those in the medical group did not (mean PDQ-39 change of -9.5 versus 0.2 , $p = 0.02$). Medication-off UPDRS-III motor scores improved by a mean of 19.5 points (from 48.0 ± 12.3 to 28.3 ± 14.7) in the DBS group and did not change significantly in the medical group. The motor diaries showed that medication-off time was reduced by 4.2 hours and on time with troublesome dyskinesia decreased by 1 hour in the DBS group, while both of these measures were unchanged in the medical group. Medication doses (expressed as levodopa-equivalents) fell by 593 mg/day (a 50% reduction) in the DBS group and by only 95 mg/day (8% reduction) in the medical group. Serious adverse events occurred in 12.8% of the DBS patients and only 3.8% of the medication-only patients; this included one fatal intracerebral hemorrhage and one suicide among the DBS patients. Overall adverse events were actually more common in the medical group (64.1% versus 50.0%). While this was the first DBS trial to include a prospective randomized control group, the lack of blinding of the patients or assessors remains a significant weakness.

PD-SURG Trial

The second large randomized trial to compare DBS to medical therapy involved 366 patients from the United Kingdom with advanced PD not adequately controlled by medications [11]. Patients were randomized in a 1:1 ratio to either DBS or medical therapy. All other treatment decisions, including selection of the surgical target, were left up to the participating physicians. Baseline characteristics included a mean age of 59 years and mean duration of PD of 11 years; these were not significantly different between groups. At 1 year, the intention-to-treat analysis demonstrated a 5.0 point improvement on the PDQ-39 summary score (the pre-specified primary outcome measure) in the DBS group versus essentially no change in the medical group (between-group difference -4.7 points, 95% CI -7.6 to -1.8 , $P = 0.001$). At 1 year, the OFF state severity as measured by the medication OFF UPDRS-III score decreased by 27.4 points in the DBS group and did not improve in the medical group (difference of -26.6 points, 95% CI -32.3 to -20.9 , $P < 0.0001$). At that point those having undergone DBS had reduced levodopa-equivalent daily doses by

34% (894 mg/day versus 1347 mg/day, difference = 453 mg/day, 95% CI 328 to 580). There was no between-group difference in the Dementia Rating Scale-II score, which worsened by 0.4 points in both groups ($p = 0.90$). Neuropsychological assessments were not available for all patients; however, analysis of available data suggested a decline in verbal fluency in the DBS group. The PD-SURG trial added to the evidence base supporting DBS in PD; however, because the DBS group included both those undergoing STN and Gpi DBS between-target differences could not be evaluated.

COMPARE Trial

For some time, the general clinical consensus held that STN DBS was not only more effective than Gpi DBS but also more likely to result in adverse cognitive and/or mood effects. The COMPARE trial was designed to evaluate between-target differences in cognitive and mood outcomes among 45 patients who were randomized to undergo either STN or Gpi DBS [12]. At 7 months post-DBS, there were no significant differences between targets on measures of mood (visual analog mood scale) or cognition (verbal fluency testing) when evaluated with stimulation at the optimal electrode contact. However, with ventral stimulation of either target adverse mood effects did often occur. The UPDRS-III motor scores improved to a similar degree in both groups. The COMPARE trial called into question the prevailing notions that STN DBS was more effective and less well tolerated than Gpi DBS.

VA Cooperative Studies Program Trial

The Veterans Affairs Cooperative Studies Program DBS trial is one of the largest randomized trials to date evaluating therapy for advanced Parkinson disease [13, 14]. Two-hundred fifty-five patients with levodopa-responsive PD, complicated by disabling motor fluctuations and/or dyskinesia for at least 3 hours daily, were randomized to undergo DBS versus best medical therapy. The 121 patients randomized to DBS were then randomized in equal numbers to either STN DBS or Gpi DBS. Because interim analysis suggested the 255 patient sample was adequate to

answer the DBS versus medication questions, additional enrollees were directly randomized to one of the two surgical targets [14]. Those initially in the medical group who later underwent DBS (117 patients) were also randomized to either STN or Gpi targets.

The initial analysis of surgery (at either target) versus best medical therapy evaluated both patient-completed motor diaries and medication OFF and ON state UPDRS-III scores at 6 months post intervention [13]. Similar to the results found in the 2006 meta-analysis of open label trials, those undergoing DBS gained a mean of 4.6 hours per day of on time without troubling dyskinesia, versus no change in the medical group ($p < 0.001$). The rater-blinded UPDRS-III evaluations showed a mean improvement of 12.3 in the surgical group versus 1.7 points in the medical group ($p < 0.001$). Dopaminergic medications decreased by 23% in the DBS group, but increased by 1% in the medical therapy group ($p < 0.001$). The PDQ-39 summary measure, a proxy for overall quality of life, was significantly improved in the DBS group compared to the medical group. Neuropsychometric testing revealed a mild but statistically significant decline in performance on measures of working memory ($P = 0.005$), processing speed ($P = 0.006$), phonemic fluency ($P < 0.001$), and delayed recall ($P = 0.03$) in the DBS group, while these measure actually improved slightly in the medical therapy group. Depression scale scores were not significantly changed in either group. Those in the DBS group had a higher incidence of falls ($P < 0.01$), gait disturbance ($p = 0.03$), depression ($p = 0.03$), and dystonia ($p < 0.01$) over the 6-month study period. Surgical site infection was the most common serious adverse event, occurring in 9.9% of the DBS patients; one fatal cerebral hemorrhage was reported. The overall incidence risk of a serious adverse event was 3.8 times higher in the DBS group than the medical group.

The 6-month outcomes described above pooled the STN and Gpi surgical groups; however a subsequent manuscript compared the change in the OFF-medication UPDRS-III scores from baseline to 24 months among those randomized to either Gpi (152 patients) or STN (147 patients) stimulation [14]. Those assessing motor exams were blind to the stimulation target. Secondary outcomes included motor diaries, PDQ-39 (quality of life), neurocognitive function, and adverse events. The intention-to-treat analysis at the 24-month time point showed that the OFF-medication ON-

stimulation UPDRS-III scores improved by 10.7 points in the STN group and 11.8 points in the Gpi group, and there was no significant between-group difference ($P = 0.50$). Patient motor diaries also suggested equivalent efficacy between targets as there were no significant between-target differences in time spent in any of the four states (OFF, ON with and without troublesome dyskinesia, and asleep). Quality of life as assessed by the PDQ-39 improved in both groups to a similar extent. There was a greater reduction in dopaminergic medication doses among those in the STN group (a 32% reduction) than those in the Gpi group (an 18% reduction) ($P = 0.02$). Required stimulation amplitudes and pulse widths were lower for the STN group compared to the Gpi group, suggesting that there may be greater battery longevity with STN stimulation. Neuropsychometric testing revealed mild decrements in measures of neurocognitive function that were similar between groups, except for the processing speed index which was reduced to a greater extent after STN DBS than Gpi DBS ($p = 0.03$). The Beck Depression Inventory II scores showed mild worsening in the STN group, but slight improvement in the Gpi group ($p = 0.02$). At the 24-month follow-up, there were no significant differences in the type or frequency of adverse events between the two study groups. Along with the COMPARE trial, the VA Cooperative trial suggested that differences between STN and Gpi DBS are indeed minor.

Thirty-six-month outcomes were reported for 159 patients who had undergone surgery per the original VA Cooperative study design; this subgroup was younger than the full sample (60.6 versus 63.2 years, $p = 0.01$) but otherwise similar [13]. The OFF medication UPDRS-III scores between baseline and the 36-month follow-up improved from 41.1 to 27.1 ($p < 0.001$) in the Gpi group and from 42.5 to 29.7 ($p < 0.001$) in the STN group. The degree of improvement was similar between targets and stable over the 36-month interval. Motor diaries also continued to show improvement above baseline in the amount of time spent ON without troublesome dyskinesia. While PDQ-39 scores had improved in both groups at 6 months, they worsened over the remaining period and by 36 months, subscales for social support and cognition were worse than at baseline. Scores on the Mattis Dementia Rating Scale and the Hopkins Verbal Learning Test did worsen in the STN group, but were unchanged in the Gpi group;

however, interpretation is complicated by differences in baseline cognitive assessments between groups. Overall, this extended follow-up demonstrated persistent motor benefit from stimulation at either target. The decline in quality of life over time was reflective of the progressive nature of PD, which causes non-motor symptoms that are not able to be treated with DBS.

Saint Jude Medical DBS Study Group Trial

In an attempt to prove the efficacy of, and gain regulatory approval for, a novel constant-current neurostimulation system, the St. Jude Medical DBS Study Group conducted a prospective, randomized, multicenter controlled trial at 15 sites in the USA [15]. One-hundred thirty six patients with advanced PD of at least 5 years duration and with greater than six hours of daily OFF time or moderate to severe dyskinesia were implanted with a bilateral STN DBS system. They were then randomized in a 3:1 ratio to immediate stimulation versus stimulation after a 3-month delay. Patients were aware of their group assignments. At the end of the 3 months, those in the DBS group experienced an additional 4.3 hours of good quality ON time versus only a 1.8 hour improvement in the control group ($p = 0.003$). The medication OFF UPDRS-III scores fell by an average of 16.1 points in the DBS group versus 2.1 points in controls (between group difference 14.0, $p < 0.0001$). Rates of adverse events were similar to those reported in previous trials. The trial added to those demonstrating the safety and efficacy of STN DBS in advanced PD.

EARLYSTIM Trial

The EARLYSTIM trial was designed to determine whether DBS at an earlier stage of PD would still be beneficial [16]. Patients with PD for at least 4 years but with motor fluctuations or dyskinesia for 3 years or less were included; this resulted in a cohort with mean disease duration of 7.5 years versus 11.7 years in the VA Cooperative trial. Motor complications had been present for a mean of 1.7 years. A total of 251 such patients were randomized in a 1:1 ratio to DBS or medical therapy. The PDQ-39 summary score for quality of life improved by 26% in the DBS group and declined by 1% in the medical group. UPDRS-III scores improved by 38% in the DBS group and did not change in the medical

group resulting in a between group difference of 8.6 ± 1.1 points favoring neurostimulation ($P < 0.001$). Motor diaries documented 1.9 hours additional time with good mobility and no troublesome dyskinesia in the DBS versus medical group. Levodopa equivalent daily doses fell by 39% in the DBS group but rose by 21% in the medical group. The Mattis Dementia Rating Scale scores were not significantly different between groups, and changes in mood as measured by two separate depression scales were in favor of the DBS group. The incidence of any adverse event was not significantly different between groups with 68 DBS patients and 56 medical patients experiencing at least one serious event. All deaths were due to suicide, two of which were in the DBS group with one in the medical group. Four additional suicide attempts were evenly split between the groups. The EARLYSTIM trial demonstrated that bilateral STN DBS improves quality of life and motor function when applied at an earlier time point in disease progression than studied in previous trials; however, the indication for surgery (namely motor fluctuation and/or dyskinesia) was the same in this trial and previous trials.

DBS in Early Stage PD

All of the above mentioned DBS trials focused on patients with advanced PD who had developed motor fluctuations and/or dyskinesia while on levodopa. However, it is unknown whether DBS would be beneficial, or possibly even neuroprotective, if applied in earlier stage disease. A pilot study of DBS in very early-stage PD, before the development of motor fluctuation or dyskinesia, has been completed and was recently published [17–19]. Thirty patients aged 50–70 who were on PD medications for at least 6 months but without motor fluctuation or dyskinesia were randomized to DBS plus best medical therapy versus best medical therapy alone. As was hypothesized by the investigators, there were no significant differences in the UPDRS-III scores between groups in either the ON or OFF medication state, but levodopa equivalent doses were lower in the DBS group at all time points. Serious adverse events were experienced by two of the DBS subjects. On the basis of this pilot trial, the investigators have designed a much larger multi center randomized trial further testing the efficacy of DBS in early stage PD.

POSSIBLE MECHANISMS OF ACTION OF DBS FOR PD

Because the effects of DBS mirror those of dopamine replacement in PD, it has been hypothesized that STN or Gpi DBS benefits parkinsonian symptoms via modulation of dopamine release to the striatum [20]. As discussed in Chapter 16, there is some evidence in animal models to suggest that STN DBS may potentiate the release of striatal dopamine. However, a growing body of evidence demonstrating that the effects of DBS are distinct from those of medication calls into question the hypothesis that symptomatic improvements after DBS are mediated mainly by alterations in dopamine release. For example, many of the above-mentioned studies show improvement in dyskinesia with DBS therapy, while dyskinesia are worsened by higher doses of dopaminergic medication. Medication-refractory parkinsonian tremor is by definition unresponsive to dopamine replacement but is however effectively treated by STN or Gpi DBS [21]. Freezing of gait may respond to dopaminergic medications, but is poorly treated with DBS. The efficacy of DBS in conditions without known neurotransmitter deficits such as essential tremor or dystonia also suggests an alternative mechanism of action. A growing body of research is focused on the possibility that high frequency DBS acts to electrophysiologically disrupt pathologic oscillations responsible for motor symptoms and thereby improve information flow through the motor circuits. In PD, it has been proposed that beta frequency oscillations in the 13–30 Hz range may be pathologically increased and that there is hypersynchronization of these subcortical circuits with the motor cortex itself [22–25]. Regardless, the fact remains that the beneficial effect of DBS in PD was empirically and somewhat serendipitously discovered and the exact mechanism by which its beneficial effects are exerted remains elusive.

SUMMARY

Parkinson disease is one of the most common neurodegenerative diseases. While its motor symptoms can effectively be treated with dopaminergic medication, as the disease progresses patients may experience motor fluctuations and dyskinesia associated

with medical treatment. For these patients DBS of the STN or Gpi may serve to attenuate the motor complications. Medication-refractory tremor and medication intolerance may be alternative indications for DBS in some PD patients. There is now a solid evidence base supporting the use STN and Gpi DBS to attenuate the severity of PD motor complications, and we are learning that the differences between these two targets are minimal. Whether DBS is helpful in early stage PD is unknown but currently under study.

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Chapter 7

Deep Brain Stimulation for Tremor

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INTRODUCTION

Tremor is the most common neurologic movement disorder. Tremor is an oscillation of a body part produced by alternating or simultaneous contraction of agonist and antagonist muscles. This movement is usually rhythmic and regular and can affect one or more body parts, including the limbs, neck, chin, tongue, or vocal cords. This chapter will address tremor in general with an emphasis on Essential Tremor (ET). Chapter 5 focuses on tremor associated with Parkinson's disease (PD).

CLASSIFICATION OF TREMOR

Tremor can be described by the body part or parts affected, the etiology, or the frequency or oscillation of the tremor. The rate or frequency of tremor is usually expressed in Hertz (Hz) with one Hz equaling one oscillation or cycle per second. Tremors are usefully and broadly classified as occurring at rest or in action.

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The rest tremor is present when the affected body part is supported against gravity and not actively contracting. Action tremors occur with voluntary contraction of muscles.

Rest Tremor

The prototypical rest tremor occurs in PD. It is often asymmetric, involves the thumb and forefinger, and is often called pill-rolling because of its resemblance to how pharmacists used to roll pills. Rest tremors are seen in idiopathic Parkinson disease, other parkinsonian disorders (multiple system atrophies, progressive supranuclear palsy, cortical-basal-ganglionic degeneration, diffuse Lewy body disease), and hereditary degenerative disorders (Huntington disease, Wilson disease, neuroacanthocytosis, neurodegeneration with brain iron accumulation type 1, Gerstmann-Sträussler-Scheinker disease, and ceroid lipofuscinosis). Rest tremor can also be seen in severe essential tremor [18].

Action Tremor

Action tremors include physiologic tremor, cerebellar tremor, task-specific tremor (e.g., primary writing tremor), and orthostatic tremor as well as dystonic, neuropathic and psychogenically based tremors. ET represents a classic action tremor.

Postural Tremor

Postural tremor occurs when maintaining a position or posture against gravity such as when the arm is extended. Postural tremors include orthostatic tremor, which is a fast (14–16 Hz) tremor affecting the legs and trunk only when standing.

Kinetic Tremor

Kinetic tremor is synonymous with movement tremor and occurs when patients are asked to perform movements like writing or using a spoon. There are task-specific kinetic tremors. Primary writing tremor, for example, is severe during the act of writing. Low in frequency (4–8 Hz) and high in amplitude, it can occur in association with writer's cramp or a focal dystonia. *Intention*

tremors are tremors that intensify when a limb is directed toward a target.

Dystonic tremors are tremors that occur with dystonia or sustained muscle contractions that frequently cause twisting and repetitive movements. They are usually less than 7 Hz, can be jerky and irregular with varying amplitude, and are often associated with specific postures. They are discussed in more depth in Chapter 7 on DBS for dystonia.

It is important to remember that patients may have more than one type of tremor. Table 7.1 summarizes the different tremor types, what activates them, and their typical frequency range in Hz.

Table 7.1 Tremor types

Diagnosis	Rest	Posture	Goal-directed movement	Frequency range (Hz)
Parkinson	X			3–6
Enhanced physiologic		X		6–12
Essential tremor		X		4–12
Cerebellar		X	X	<5
Task-specific			X	4–8
Orthostatic		X		>13
Dystonic		X	X	<7
Neuropathic		X		3–6
Psychogenic				4–12

TREMOR PATHOPHYSIOLOGY, HISTORY, AND BACKGROUND

Rest Tremor

Injury to the midbrain (superior cerebellar peduncle, substantia nigra, or red nucleus) can cause a rest tremor called a rubral tremor, Holmes tremor, or cerebellar outflow tremor. This tremor may also have a postural, action, and intention component. Exposure to dopamine-receptor blocking drugs can cause a tardive tremor that can occur at rest. Myorhythmia is a slow rhythmic movement that is present at rest and has been seen in brainstem stroke, Wilson's disease, Whipple's disease, and cerebellar degenerations [18].

Action Tremor

Every individual has what is called physiologic tremor, a tremor that is usually not visible. Anything that stimulates the nervous system can result in a visible action tremor, called an “enhanced physiologic tremor” [39]. Enhanced or exaggerated physiologic tremor is both postural and kinetic and ranges from 6 to 12 Hz. It can be caused by stress (anxiety, emotion, exercise, fatigue, fever), drugs, and endocrine disorders (e.g., hypoglycemia, thyrotoxicosis, pheochromocytoma). Common drugs that cause this type of action tremor include (1) beta-agonists like theophylline, terbutaline, epinephrine; (2) dopaminergic drugs, such as levodopa and dopa-agonists; (3), stimulants; (4) psychiatric drugs, including antidepressants and neuroleptics; (5), methylxanthines, like coffee and tea; and (6) multiple others of different categories like amiodarone, valproate, cyclosporine, and interferon. Drug-induced tremor is usually temporally related to drug onset and often has a dose-response relationship with the causative drug. Toxins known to cause enhanced physiologic tremor include mercury, lead, arsenic, bismuth, bromide, and alcohol withdrawal. An enhanced physiologic tremor should always be considered in the differential diagnosis of a patient with a postural and kinetic tremor.

Essential Tremor

As stated earlier ET is the classic action tremor. It usually consists of both a postural and an action tremor with a frequency varying between 4 and 12 Hz. The term “essential” is synonymous with idiopathic. When there is a family history of tremor, ET is referred to as “familial tremor.” The definition of ET is a subject of controversy [45], and there has been no consensus as to whether it is a symptom, a syndrome, or a specific disease.

The prevalence and incidence of ET increases with age [38]. Estimates of prevalence vary from 4% to 39%, a range that reflects the lack of a reliable diagnostic test, undiagnosed patients with mild disease, and ascertainment bias.

There is no disease specific marker for ET, so the diagnosis is clinical. The primary criteria are bilateral postural tremor, with or without kinetic tremor of the hands and forearms, and the absence of other neurologic signs. Rest tremor is not included in

the classification of ET, although, as noted earlier, patients with severe ET can have a rest tremor. ET can include tremor of body parts other than the upper limbs. Secondary criteria include a positive family history, long symptom duration, and a beneficial response to alcohol. Froment's sign or cogwheeling in the absence of rigidity can be seen in ET. A mild disturbance in tandem gait with no other abnormalities can be seen in advanced cases. Head tremor can occur without signs of head tilt or turning, which distinguishes it from dystonic tremor. Other exclusions include the causes of enhanced physiologic tremor—specifically, concurrent or recent exposure to tremor-inducing drugs, trauma to the peripheral and central nervous system, sudden onset or stepwise deterioration consistent with vascular disease, and historical or clinical evidence of psychogenic origins. A duration of more than 5 years is required for “definite” ET, and a duration of more than 3 years is required for “probable” ET [4].

Other motor features seen in patients with ET, but not considered part of the standard classification, include gait ataxia, eye-motion abnormalities, and postural instability. Non-motor features described in patients with ET include memory and executive problems, anxiety, depression, social phobia, olfactory deficits, and hearing loss. A large clinical series of patients with ET identified five phenotypes: (1) classical ET hand tremor, (2) ET with head tremor, (3) ET with jaw tremor, (4) ET with tongue and voice tremor, and (5) ET with tremor of the trunk and legs and feet [47, 51].

Essential Tremor and PD

Distinguishing ET from PD can be a diagnostic challenge [48]. Both are very common disorders, can coexist in one patient, and can have overlapping clinical features. There is some controversy regarding the association of ET and PD. The use of dopamine transporter (DaT) single photon emission tomography (SPECT) has led to the term SWEDDs (Scans Without Evidence of Dopaminergic Deficit) for patients with a rest and postural tremor who do not develop PD. Some neurologists believe that these patients have a benign form of PD, and others believe they may be a subset of ET or adult-onset dystonic tremor.

The entity described as “benign tremulous parkinsonism” supports the relationship between ET and PD. It is characterized by predominant tremor, very mild parkinsonian features, slow progression of disease, and sometimes limited response to levodopa. Like ET, benign tremulous parkinsonism may respond very well to thalamic deep brain stimulation [25].

Etiology of ET

Approximately 50% of all patients with ET have an autosomal dominant pattern of inheritance. The genetics of ET is complex and heterogeneous [3, 28, 34]. This limits our understanding of the causes and mechanisms of ET. Cause and mechanism are the subject of ongoing investigations.

Linkage studies in families with ET have identified genetic loci on chromosome 3q13 (ETM1), 2p22-p25 (ETM2), and 6p23. However, other families with ET are not linked to these loci, and no genes with causative mutations have been reported. Exome sequencing has identified mutations in the FUS gene as the cause of ET in a multigenerational family with ET [40]. A different FUS mutation causes a form of familial amyotrophic lateral sclerosis. Genome-wide association studies have implicated genes that are involved in oligodendrocyte differentiation and axonal myelination. Other studies have demonstrated an association with the glial glutamate transporter gene.

Pathophysiology of ET

The pathophysiology of ET is uncertain [36]. It is thought to occur from the abnormal oscillations within the thalamocortical and olivocerebellar loops. A mouse model of ET suggests the disorder may be from a widespread disorder of motor control.

The pathology in ET also appears to be heterogeneous. Pathologic findings have been seen in the Purkinje cells of the cerebellum [1]. These include a modest reduction of Purkinje cells, Purkinje cell axonal swellings (torpedoes), changes in axonal shape, and changes in axonal connectivity. Torpedoes consist of accumulation of disoriented neurofilaments and have been described in other disorders of the cerebellum like the cerebellar ataxias. Depletion of pigmented neurons in the locus coeruleus, the nucleus in the pons associated with norepinephrine, and

cerebellar gliosis have been reported pathologic changes in brains of patients with ET [10, 37].

Diffusion tensor MRI, a technique to assess gray and white matter damage in neurodegenerative diseases, has shown changes in the dentate nucleus and the superior cerebellar peduncle of patients with familial ET [41]. Lewy bodies in the brainstem and cerebellum have also been seen, a finding that raises a pathologic link to other Lewy body diseases like PD.

Studies using voxel-based morphometry based on high-resolution T1-weighted MRI to compare gray and white matter density have shown conflicting results in patients with ET [9, 44]. One study showed no decreases in cerebellar gray matter volume. Another showed atrophy of the cerebellar vermis in patients with head and arm tremor but not in patients with tremor isolated to the arm [7, 42].

Kinetic Tremor

Kinetic (i.e., intention or goal-directed) tremors are seen in disorders of the cerebellum and its outflow pathways. Kinetic tremor is associated with multiple sclerosis, trauma, stroke, Wilson's disease, neurodegenerative disorders, and certain drugs and toxins. Cerebellar tremors can also be postural. In severe cases, the tremor can occur at rest. The typical frequency of a cerebellar tremor is low (3 to 4 Hz). Titubation (rhythmic oscillation) of the head may occur in presence of cerebellar tremor and other cerebellar signs like ataxia and dysmetria distinguish this from ET. Midbrain lesions also are associated with kinetic tremors.

Neuropathic Tremor

Neuropathic tremor has been associated with large-fiber neuropathies including hereditary neuropathies and acute and chronic inflammatory demyelinating polyneuropathies. This type of tremor tends to involve distal muscles and can be irregular with variable amplitude.

Psychogenic Tremor

Psychogenic tremor can be a diagnostic challenge. Features that suggest psychogenic tremor include abrupt onset, static course,

spontaneous remission, different combinations of rest, postural, and kinetic tremor, changing amplitude and frequency, poor response to antitremor drugs, tremor that increases with attention and decreases with distraction, absence of other neurologic signs, and improvement with psychotherapy [32].

DBS TARGETS AND SURGICAL PROCEDURE

DBS Targets

Surgical options for the treatment of tremor include stereotactic radiofrequency thalamotomy, gamma knife thalamotomy, and deep brain stimulation (DBS). The most frequent anatomical DBS target for medically refractive tremor is the ventral lateral or the ventral intermediate (VIM) nucleus of the thalamus (Fig. 7.1) [31, 33]. VIM receives afferent input from the contralateral deep cerebellar nuclei (primarily the dentate nucleus) and sends output to the primary motor cortex. This nucleus was the target in ablation surgery for patients with tremor associated with ET or PD. Benabid introduced clinical DBS in 1987 for the treatment of medically refractive tremor in patients with PD and ET [5]. DBS of VIM is used as an alternative to thalamotomy with the advantage of being reversible. DBS can be performed bilaterally without the unacceptable side effects of bilateral ablative therapy, such as irreversible dysarthria and dementia. DBS also has the advantage of adapting the programming parameters to the status of the patient, which may minimize adverse effects. While VIM is still used as a target for patients with tremulous PD, the subthalamic nucleus (STN) and the globus pallidus interna (Gpi) have become the preferred targets to treat the rest tremor of PD with the added benefit of treating the slowness of movement and rigidity. VIM is still used as a target for patients with tremulous Parkinson disease [24, 25, 30].

In addition to VIM other potential targets for tremor include the STN, the zona incerta and the surrounding white matter tracts [6, 43, 46]. The zona incerta is located medially to the internal capsule, ventral to the thalamus, and is contiguous with the thalamic reticular nucleus. The nucleus separates the lenticular fasciculus from the thalamic fasciculus (also known as the “field H1 of Forel”). The caudal or motor part of the zona incerta (cZI)

has been explored as a possible DBS target (Fig. 7.2). One prospective study demonstrated bilateral cZI DBS improved both proximal and distal limb tremor compared to just the more distal tremor with VIM stimulation. Stimulation of the posterior subthalamic area (PSA), including the zona incerta, Forel field H, and the prelemniscal radiation (Raprl) have also demonstrated benefit for ET (Fig. 7.3). Based on ablation therapy, other thalamic nuclei targets for have included the ventral oralis anterior (Voa) and ventral oralis posterior (Vop) in combination with VIM [27] (Fig. 7.4).

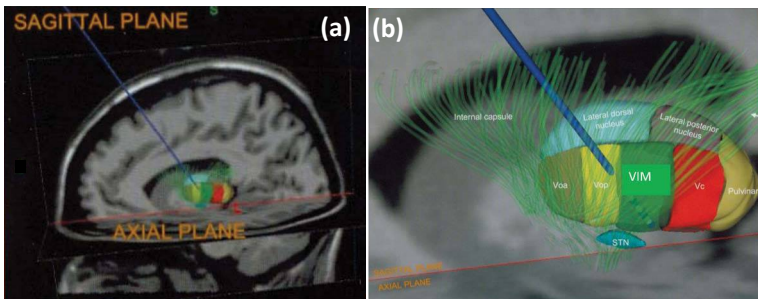


Figure 7.1 (a) MRI with a 3D color image of the thalamus; (b) the ventral intermediate (VIM) nucleus of the thalamus is highlighted in green.

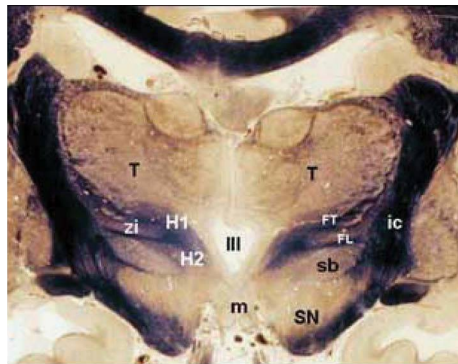


Figure 7.2 Coronal section through the thalamus and midbrain. The zona incerta (zi) is considered a potential DBS target for tremor. T = thalamus, III = third ventricle, ic = internal capsule, zi = zona incerta, sb = subthalamic nucleus, SN = substantia nigra, FT and H1 = thalamic fasciculus or field H1 of Forel, FL or H2 = lenticular fasciculus or field H2 of Forel, m = mammillary bodies.

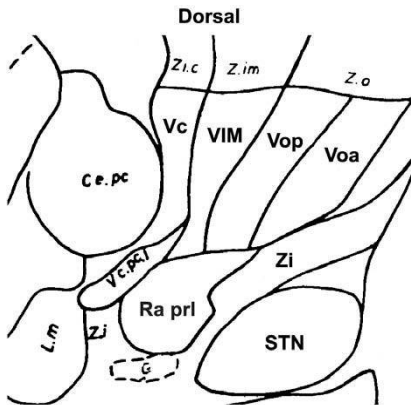


Figure 7.3 Sagittal section of the ventral tier of the thalamus. The posterior region of the subthalamic nucleus (STN), zona incerta (Zi), and prelemniscal radiations (Ra prl) have all been selected as potential DBS targets for ET. Vc = ventral caudalis, VIM = ventral intermediate, Vop = ventral oralis posterior, Voa, Ventral oralis anterior. Modified from [54], Plate 43.

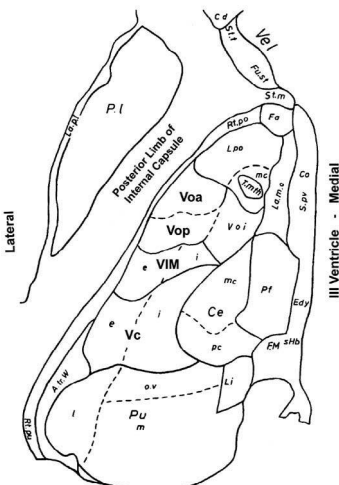


Figure 7.4 Horizontal section of the thalamus 2 mm above the anterior commissure-posterior commissure line (Hassler nomenclature). Modified from [54], Plate 53.

Studies have shown that the optimum DBS target for ET varies among patients. Reasons that might account for this variability include limitations of existing surgical atlases, anatomical imaging, and variation in patient anatomy, all of which can affect accurate electrode placement, as well as variation in tremor pathophysiology, and the heterogeneity of ET. Diffusion tractography has demonstrated the cerebellothalamocortical motor pathway is involved in tremor, regardless of its etiology. It is not known whether the cerebellothalamocortical motor pathway is involved in the suppression or production of tremor but it is the principle DBS tremor target [8].

Patient Selection

The most important factor in achieving favorable surgical outcomes in DBS surgery is careful patient selection. This is best done by a multidisciplinary team. The clinical evaluation of the tremor is important and the diagnosis should be confirmed. Drug-induced tremor or tardive tremor should be excluded in the clinical diagnosis. Candidates for DBS should be restricted to those patients with disabling action, postural, or rest tremors that significantly impair the ability to carry out daily tasks. The patient's tremor should be medically refractory, which usually means that maximum tolerated doses of beta-blockers and primidone have not been effective or were poorly tolerated. A positive family history of tremor and a decrease in tremor on ingestion of alcohol are positive signs that DBS may be helpful. An important clinical caveat is that alcohol can reduce tremor while the patient is drinking but can exacerbate it when the patient stops drinking.

If the patient has a Parkinson tremor or dystonic tremor, the choice of target becomes an issue. Benign tremulous Parkinson disease may do very well with VIM as the target but STN and GPi should be considered for other manifestations of PD. The GPi may be the preferred target for dystonic tremor. The patient's neuropsychological and psychiatric status will also influence the risk-benefit. For example, a reduction in the patient's tremor may be of limited benefit if their dementia or depression become incapacitating. DBS may exacerbate cognitive or psychiatric problems, and post-surgical programming requires accurate feedback from the patient [11, 12].

Tremor rating scales are often used for screening, evaluation, and assessing response to therapy [2, 16, 19]. For example, the Fahn-Tolosa-Marin Tremor Rating Scale can be used by clinicians to evaluate tremor in the head and in the upper and lower extremities at rest and in extended positions. The modified Bain rating tremor scale [2] is an example of a rating scale completed by the patient to assess the effects of tremor on activities of daily living. There are 25 activities listed (e.g., ability to use a spoon, hold a cup, write a letter, brush your teeth) which the patient rates using a 4-point scale. In addition to these subjective measures, quantitative computerized analysis of tremor is available at tertiary care facilities and can include accelerometry and electromyography (EMG).

Surgery

As described in Chapter 1, the surgery for DBS is often, but not always, a staged procedure with the placement of the intracranial electrode(s) first and the subcutaneous placement of the connecting wires and battery for the implanted pulse generator (IPG) during the second stage. The first stage involves the attachment of the stereotactic head frame under local anesthesia. Once the head frame is affixed, the patient has an MRI of the head for image-guided target determination. The magnetic resonance imaging data is transferred to the stereotactic navigation system. Based on this image and image fusion with the Schaltenbrand-Wahren atlas, the *x*, *y*, and *z* coordinates for the target nucleus and the trajectory of the probe are determined.

Microelectrode electrode recording is done to provide electrophysiologic confirmation of the target. When the target is reached, the DBS leads are placed and intraoperative stimulation is then performed to assess efficacy and the presence of any adverse effects. Intraoperative imaging to confirm lead location can involve fluoroscopy and magnetic resonance imaging. The patient is usually anesthetized for the placement of the connecting wires and IPG.

In addition to the fact that the surgery is reversible, programming adaptability of DBS is a major advantage of DBS over ablative therapy. The DBS electrode has four electrodes and one or all can be configured (monopolar or bipolar) to optimize

the clinical response. Post-surgical adjustments can be made in the amplitude of the charge, pulse width, and frequency to maximize stimulation of the motor target and minimize stimulation outside the target (Fig. 7.5). Following successful DBS, antitremor drugs can be reduced or eliminated. DBS is more expensive than ablation surgery, and there is the added cost of programming and maintaining the IPG device. However, given that DBS does not destroy tissue, can be performed bilaterally, and is programmable, it is preferred to ablation therapy.

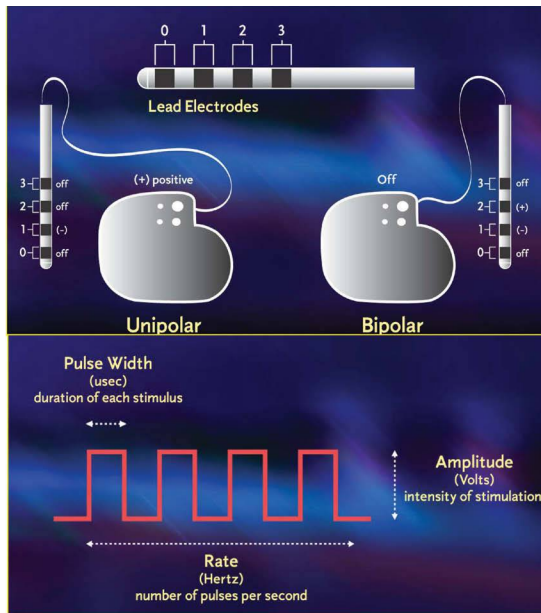


Figure 7.5 DBS electrodes and programming options. Diagram demonstrating the four electrode sites on the lead electrode. Programming options include electrode configuration, manipulation of amplitude, pulse width, and rate.

NEUROPHYSIOLOGY, MECHANISM

The mechanism of deep brain stimulation is not completely understood [14, 50]. The effects of DBS are similar to ablation therapy suggesting a reversible inhibition of the target site. High-frequency stimulation can produce synaptic or axonal failure, and perhaps this is what produces the “electrical” ablative effect.

Suggested mechanisms for DBS include depolarization blockade, jamming of neural activity, channel blockade, neuronal energy depletion, synaptic failure, anterograde effects, retrograde effects, activation of inhibitory neurotransmission, inactivation of excitatory neurotransmission, effects on non-neuronal cells, and effects on local concentration of ions or neuroactive molecules. In addition to inhibition, stimulation causes excitation, changes in firing rates and patterns, changes in neurochemistry, changes in blood flow, effects on neurons and astrocytes, and possibly encourages neuroplasticity.

OUTCOMES, IMPORTANT TRIALS

The results of VIM DBS for ET have been highly effective with satisfactory results in over 90% of patients [15, 17, 23, 35]. The most significant effect is in the contralateral arm. Head and voice tremor are more difficult to control but a reduction in these midline tremors has been achieved. Most patients have a dramatic improvement in their functional abilities with reports of moderate to marked improvement noted in 80% of patients.

Several studies looking at the long-term outcomes of thalamic DBS for tremor have shown favorable results. A multicenter European study looking at VIM surgery in Parkinson disease found the tremor remained well controlled 6 years after surgery [25]. Another multicenter study recommended unilateral stimulation for long-term management of ET, noting that bilateral stimulation resulted in a higher frequency of dysarthria and incoordination. Complicating the interpretation of this study is the incoordination seen in some groups of patients with ET who do not have DBS.

Although the long-term benefits of thalamic DBS for tremor have been demonstrated, in a small percentage of patients, tremor returns. It is not known whether this is a result of developing tolerance, an indication of disease progression, or if other factors are involved [20, 26].

There is clinicopathologic follow-up on a patient who had thalamic stimulation for 12 years [13]. The minimum foreign body reaction and gliosis around the patient's electrodes 12 years after implantation support the long-term safety of DBS.

In their practice parameter for therapies in ET, the American Academy of Neurology concluded that DBS of the VIM thalamic nucleus effectively reduces contralateral limb tremor in medically refractory ET [52, 53]. In their 2005 and updated 2011 paper, there was insufficient data to recommend DBS for head and voice tremor, but it was noted that some studies demonstrate that bilateral VIM DBS was able to reduce these midline tremors. Neuropsychological and quality of life outcomes one year after unilateral thalamic stimulation demonstrated favorable outcomes. This included effects on cognition, mood and quality of life measures. A significant reduction in anxiety was also noted [12, 22].

The outcome of VIM stimulation for tremor in patients with multiple sclerosis is less and more variable than for patients with ET. This inconsistent result may reflect the variability of demyelinating lesions and underlying ataxia that is not treated with DBS [49].

COMPLICATIONS

The complications of DBS surgery for tremor are low, around 3–4% [21]. By comparison, adverse effects associated with thalamotomy occurred in 14% to 47% of patients with persistent adverse effects in 16%. Surgical complications for both procedures include hemorrhage, seizure, and permanent neurologic deficit. For DBS, specifically, hardware-related complications include infection, device malfunction, lead fracture, lead erosion, and lead misplacement or migration.

A retrospective analysis of over 300 DBS patients with diverse movement disorders over a ten year period from Baylor College of Medicine concluded that DBS is a proven and safe therapy for the treatment of medically refractive movement disorders [29]. Their overall intraoperative adverse events were less than 2.5% and included vasovagal response, syncope, cough, intraventricular hemorrhage, intracerebral hemorrhage, arrhythmia, confusion, anxiety, laceration of the soft palate, and a transient ischemic attack. The two most common adverse events in the perioperative period (<2 weeks) were headache and confusion, which were reported as benign and transient. The most common long-term adverse events (3–4%) included infection, dysarthria, cognitive

dysfunction, and worsening gait. Long-term adverse events, which occur in less than 1% of patients included depression, headache, psychogenic tremor, urinary incontinence, blepharospasm, emotional lability, insomnia, metallic taste, and suicide.

The regional anatomy of the VIM is important in understanding stimulation-related complications. The ventral caudal nucleus of the thalamus lies posterior to VIM and stimulation of this sensory nucleus can cause paresthesias. Stimulation of the internal capsule involving the corticospinal and corticobulbar tracts can elicit tonic muscle contractions and dysarthric speech. Other stimulation-related complications include diplopia, cognitive changes, depression, mania, suicide, anxiety, panic attacks, aggression, and pseudobulbar affect. Fortunately, most of the stimulation-related adverse effects can be managed with changes in the programming parameters.

CONCLUSION

Tremor is a very common, heterogeneous, and often disabling movement disorder affecting employment, activities of daily living, and social function. Pharmacotherapy is typically the initial treatment, but it is estimated that 30% to 50% of patients with ET will be refractory to medications. DBS for tremor has been proven a safe and efficacious therapy for medically refractive tremor. Many questions remain regarding the diagnosis and treatment of tremor, but anticipated advances in our understanding of the disease and the future of neuromodulation are likely to allow us to continue to improve therapies for our patients.

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Chapter 8

Deep Brain Stimulation for Dystonia

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INTRODUCTION

Dystonia is an uncommon but often debilitating movement disorder with a worldwide prevalence of primary dystonia of 16.43 per 100,000 [1]. The term “dystonia” was first used in 1911 by Oppenheim to describe four patients he treated for muscle spasms and twisted postures [2]. Over time, the definition of dystonia has been refined but it continues to refer to movement disorders that involve involuntary, sustained muscle contractions causing repetitive twisting movements that result in abnormal postures [3].

Dystonia is classified by its clinical features and broad-based etiological categories (Table 8.1). The five important clinical characteristics are: age at onset, body distribution, temporal pattern, coexistence of other movement disorders, and neurological manifestations. The etiological axis is divided into identifiable nervous system pathology at either a gross, microscopic, or molecular level of known or unknown cause and pattern of inheritance (inherited acquired or of unknown cause) [4].

Deep Brain Stimulation: Indications and Applications

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Table 8.1 Classification of dystonia

Axis I: Clinical features
<i>Age at onset</i>
Infancy: birth to 2 years
Childhood: 3 to 12 years
Adolescence: 13 to 20 years
Early adulthood: 21 to 40 years
Late adulthood: greater than 40 years
<i>Body distribution</i>
Focal: only one body region is affected
Segmental: two or more contiguous body regions affected
Multifocal: two noncontiguous or more body regions affected
Generalized: trunk (key feature to classify as generalized) and at least 2 other sites are involved
Hemidystonia: Body regions restricted to one body side are involved
<i>Temporal pattern</i>
Disease course
Static
Progressive
Variability
Persistent
Action-specific
Diurnal
Paroxysmal
<i>Associated features</i>
Isolated or combined with another movement disorder
<i>Occurrence of another neurological manifestation</i>
Axis II: Etiology
<i>Nervous system pathology</i>
<i>Inherited or acquired</i>

Source: Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013, 28: 863–873.

Treatment of dystonia is very difficult. Medications are often of limited clinical benefit and can have significant adverse effects [5]. Functional neurosurgery was thus attempted as early as the 1950s and included thalamotomy and pallidotomy. Unfortunately, both of these procedures also had significant potential morbidity, particularly when performed bilaterally. The success of deep brain stimulation (DBS) in Parkinson's disease led to trials of DBS for dystonia, primarily targeting the Globus Pallidus interna (GPi). Today, DBS has become the primary neurosurgical procedure for dystonia, and it is recommended over pallidotomy by the authors of the most recent 2011 European Federation of Neurological Science Guidelines [6].

BACKGROUND AND PATHOPHYSIOLOGY

Oppenheim's original 1911 paper described four unrelated children and adolescents who presented with muscle spasms and muscle tone that alternated between hypotonia and hypertonia and resulted in progressive, fixed, twisted postures which worsened upon walking and presented in the absence of weakness, sensory loss or atrophy [2, 7]. Oppenheim suggested either *dysbasia lordotica progressiva* or *dystonia musculorum deformans* as possible names for the condition, but particularly favored "dystonia" as most appropriate due to the concurrence of hypotonia and hypertonia.

In 1975 it was recognized that in addition to generalized dystonia, focal symptoms developing in adulthood such as blepharospasm and torticollis could also be considered forms of dystonia [8]. This resulted in a refinement in 1976 by Fahn and Eldridge of the classification of dystonia as: (1) primary with or without a hereditary pattern; (2) secondary with other neurological or environmental cause; and (3) psychologically based [9]. At the same time, a classification based upon distribution of dystonia as either focal, segmental or generalized was also proposed [10].

In 1984 the Dystonia Medical Research Foundation formed a committee that provided the first consensus definition of dystonia, which stated, "*Dystonia is a syndrome of sustained muscle contraction, frequently causing twisting and repetitive movements or abnormal postures*" [8, 11, 12]. Subsequently the classification

was expanded to include “dystonia plus” syndromes, a term that refers to dystonia that is associated with other neurological symptoms such as parkinsonism [13].

At the Fifth International Dystonia Symposium in 2013, the definition and classification of dystonia was further revised. Dystonia was defined as “... *a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation*” [4].

The impact of genetic abnormalities ranges across a broad spectrum, from monogenic forms with penetrance ranging from reduced to full penetrance in which all carriers are affected, to susceptibility genes. Genetic abnormalities appear to have an effect on the efficacy of DBS in dystonia. For example, patients with DYT1 mutations generally get more benefit from DBS than patients with non-DYT1 forms of dystonia. Currently, genetic abnormalities are classified by the DYT system which was initially designed to indicate genomic regions that had been linked to a specific disorder but for which the actual causative gene was unknown. The implication is that once the actual gene was identified, the DYT locus would be withdrawn. However, this has not occurred. There are currently 25 DYT loci, which have been assigned in chronological order, and the number is steadily increasing. Recently it has been proposed that we do away with numbering and that only confirmed genes be included in the list of DYT_s [14]. However, in this chapter will use the current system (Table 8.2).

Of the pure dystonia’s genetic abnormalities in the following genes have been described [15] : DYT1/TOR1A, DYT6/THAP1, DYT23/ANO3, DYT4/TUBB4A. DYT1/TOR1A was first discovered in 1990 in the Ashkenazi Jewish population, although the TOR1A (Torsin Family 1, Member A) gene responsible was not identified till 1997, 7 years later [16, 17]. Symptoms can be mild or severe and typically began at a mean age of 13 with twisting of a limb followed by progression to other limbs and the torso, but sparing the neck and face [18]. This is an inherited, autosomal dominant form of dystonia [15, 19, 20].

Table 8.2 Important forms of monogenic dystonia

Symbol	Gene	Inheritance pattern	Clinical features
DYT1	TOR1A	Autosomal dominant	Early-onset generalized dystonia
DYT4	TUBB4	Autosomal dominant	Non-DYT1 dystonia; Whispering dystonia
DYT5a	GCH1	Autosomal dominant	Dopa-responsive dystonia
DYT5b	TH	Autosomal recessive	Dopa-responsive dystonia
DYT6	THAP1	Autosomal dominant	Adolescent-onset, mixed phenotype
DYT11	SGCE	Autosomal dominant	Myoclonus-dystonia
DYT12	ATP1A3	Autosomal dominant	Rapid-onset dystonia-parkinsonism
DYT23	C1Z1	Autosomal dominant	Adult-onset cranial-cervical dystonia

DYT6/THAP1 was assigned a locus in 1997, but the gene itself, THAP1, was not identified until 2009 and includes a variety of mutations [21, 22]. THAP1 mutations are inherited in an autosomal dominant fashion, but patients tend to present at an older age than those with DYT1/TOR1A and they tend to have cranio-cervical or focal dystonia, particularly affecting the upper limbs [23, 24].

In recent years, four genes have been implicated in adult-onset segmental dystonia: DYT25/GNAL, DYT24/ANO3, DYT23/C1Z1, DYT4/TUBB4. However, to date, only DYT25/GNAL has been independently confirmed [25–29]. A number of genetic mutations have been identified in important dystonia plus syndromes. Important dystonia plus syndromes can be found in Table 8.2 and include: DYT11/SGCE, DYT12/ATP1A3, DYT5a/GCH1, DYT5b/TH.

Myoclonus-dystonia is the most common dystonia plus syndrome and is caused by mutations in DYT11/SGCE [30]. This disorder typically presents in childhood and is characterized by a combination of brief myoclonic jerks often affecting the neck, trunk and upper limbs, which typically dominates the clinical picture and can be either focal or segmental dystonia [31, 32].

Rapid onset dystonia-parkinsonism has been associated with mutations in DYT12/ATP1A3 and typically has an onset in

adolescence or young adulthood and presents in the setting of physical or psychological stress. It can progress to dystonia and parkinsonism in the course of several hours or weeks [33, 34]. There is often a rostrocaudal gradient, with prominent bulbar symptoms, the arms less involved, and the legs the least affected. Unfortunately, despite the parkinsonian symptoms, patients do not respond to levodopa [34]. A similar disorder DYT3 also presents with dystonia and parkinsonism but is X-linked and endemic to the Philippines. The genetic abnormality has not yet been convincingly proven, although it is possibly within TAF1 gene [35].

Dopa-responsive dystonia can be caused by either autosomal dominant or recessive mutations in DYT5a/GCH1 and DYT5b/TH, respectively [36, 37]. DYT5a is the more commonly inherited form with only a limited number of DBY5b cases reported in the literature. Patients typically present in childhood with lower limb dystonia, diurnal fluctuations, and a gradual generalization of symptoms and dramatic response to levodopa treatment [38–40]. As is common among recessive disorders, patients with TH mutations typically have a more severe phenotype. They may present in infancy as a progressive hypo-kinetic-rigid syndrome with dystonia or as a more complex neonatal-onset encephalopathy associated with a variety of signs [41].

Disease pathophysiology

Despite recent strides in our understanding, the exact pathophysiology underlying dystonia remains uncertain. Currently there are three main interdependent theories: (1) loss of neural inhibition; (2) sensory dysfunction; and (3) alterations in synaptic plasticity [42]. These abnormalities are thought to result in changes in the basal ganglia thalamic circuit (BGTC) and also possibly, the cerebellothalamocortical (CBTC) circuitry [43].

Loss of inhibition has been extensively studied in dystonia, particularly in focal dystonias. Studies of transcranial magnetic stimulation show changes in the slope of motor-evoked neural potential recruitment curves and a decrease in intracortical neural inhibition [44–47]. Abnormalities in inhibitory circuits have been reported throughout the central nervous system [48]. In focal hand dystonia, abnormalities in surround inhibition (the inhibitory command for undesired movement) have been found, although

the mechanism underlying surround inhibition remains unknown [46].

A variety of sensory abnormalities have been found in patients with dystonia, such as impairments in discriminating sensory input in both spatial and temporal domains [49]. Abnormalities in temporal discrimination have also been reported in relatives of patients with generalized dystonia, although it remains to be seen if this is just an epiphenomenon [50]. Sensory tricks, such as using a simple tactile gesture to temporarily stop the dystonia are often seen in patients with cervical dystonia, adding to the suggestion that dystonia includes abnormal sensorimotor integration [51, 52].

Some patients appear to develop dystonia from over-training, that is repetitive excessive training of a specific task. In these patients, maladaptive plasticity appears to play an important role in focal dystonias [53, 54]. For example, in a primate model of focal hand dystonia caused by overtraining, the primary somatosensory cortical zone was markedly degraded. However, because not all patients who train extensively develop dystonia, it has been suggested that other factors must be at play, such as a use-dependent environment and abnormal plasticity within sensorimotor loops [55, 56].

GPI is the main output nucleus of the basal ganglia projecting via the thalamus to the cortex. The importance of the basal ganglia in the pathophysiology of dystonia was originally proposed because of the success of pallidotomy for the treatment of dystonia [57, 58]. Microelectrode recordings in the GPI have shown several patterns of abnormal neuronal firing within the BGTC [59] and that abolishing this activity can result in some improvement in dystonic symptoms [60]. Whereas in normal primates GPI neurons fire tonically, in dystonic patients neurons have been found to fire in irregularly grouped discharges with intermittent bursts [60–62]. Thus, there are differences not only in the rate of discharge but also in the pattern of neuronal firing in the BGTC of patients with dystonia. It has been postulated that striatal over-activity accounts for these observed changes [43]. There is increasing evidence that not only is the BGTC important but also the CBTC in that cerebellar output has been found to cause changes in the BGTC [63–65].

DBS TARGET AND SURGICAL PROCEDURE

DBS for dystonia was first described in 1977 by Mundinger, and subsequent patient series were then reported in 1987, 1999, and 2000 [66–70]. Identifying the selection criteria for DBS has been hampered by the complex, heterogeneous nature of dystonia and the fact that most published studies of DBS for dystonia consist of small case series with differing entry criteria and neurosurgical techniques [71, 72]. Although there is some conflict in the literature about the benefit of DBS for dystonia in part due to the wide variety of dystonia types, it appears that patients with primary dystonia have better outcomes than those with secondary dystonia [72]. A meta-analysis of patients with generalized dystonia suggests that patients who have a shorter duration of symptoms and DYT1 abnormalities have better improvement in symptoms [73]. In children, there is evidence that the proportion of their life spent with either primary or secondary dystonia has an inverse effect on the efficacy of GPi-DBS [74].

Prior to surgery, candidates for DBS are typically evaluated by a multi-discipline team consisting of neurologists, neurosurgeons, psychiatrists, and nurse specialists, and have an MRI of the brain [75]. Standardized rating scales, such as the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), which is used in most published studies of dystonia to assess the motor impairment and its resulting disability, are usually administered to provide baseline measures of function [76].

GPi has become the standard and most effective DBS target for dystonia, although other targets include the subthalamic nucleus and the ventral intermediate nucleus thalamus [77–79]. As noted above, the GPi is the main output nucleus of the basal ganglia, and the motor circuits are located in the posteroventral lateral portion of the nucleus [43]. Electrode position within the GPi affects outcomes, and posteroventral GPi stimulation has been found to be the most efficacious target for dystonia of the arm and trunk. However, one study found no difference between posteroventral and anterodorsal stimulation [80].

DBS for dystonia is typically performed with the patient under general anesthesia, to prevent movement while in the head-frame, and MR imaging-based stereotaxy is used to locate the target [81, 82]. However, awake MR imaging-based stereotaxy,

microelectrode recording, and intraoperative test stimulation to check thresholds for stimulation-induced adverse effects may result in better clinical outcomes in those patients who are able to tolerate an awake procedure [83].

POSSIBLE MECHANISM OF ACTION

Although the mechanism of action of GPi stimulation for dystonia is not known, it has been postulated that GPi-DBS causes desynchronization of excessive pallidal activity [42]. In contrast to Parkinson's disease and essential tremor, the effects of DBS for dystonia take several months to accumulate suggesting that DBS-evoked changes may also be related to gradual change in brain plasticity [84]. A study of the blink reflex in patients with primary torsion dystonia found that increased brainstem neuronal excitability at pre-surgical baseline decreased progressively toward normal levels of excitability with GPi-DBS, suggesting a change in brain plasticity [85].

Other studies looking at changes induced by GPi-DBS have assessed pathophysiologic responses using transcranial magnetic stimulation, which is used to monitor changes in short-latency intracortical inhibition (a measure of GABA_A-ergic corticocortical connections) and long-term potentiation-like synaptic plasticity [86]. Prior to DBS, short-latency neural inhibition was reduced, and plasticity increased in patients with dystonia. Over a period of several months, short-latency neural inhibition increased, and synaptic plasticity, which was initially absent, increased toward normal levels. It is therefore likely that GPi stimulation effects in dystonia are due to alteration in brain plasticity.

DBS OUTCOMES

Primary Dystonia

There has been only one prospective, multicenter study evaluating the efficacy of bilateral GPi-DBS for generalized primary dystonia [84]. The 22 patients in the study underwent bilateral implantation of the posterolateral ventral part of the GPi, and the BFMDRS was used to evaluate the efficacy of neurostimulation.

There was significant improvement in the motor score from a pre-surgical mean of 46.3 ± 21.3 to a mean post-surgical mean of 21.0 ± 14.1 ($P < 0.001$) at 12 months post-surgery with lower scores representing less dystonia and therefore improvement. The BFMDRS disability score also showed significant improvement from an average score of 11.6 ± 5.5 before surgery to 6.5 ± 4.9 at 12 months post-surgery ($P < 0.001$). Five adverse events occurred, each of which resolved without serious sequelae.

There has been only one randomized, blinded study of bilateral GPi DBS for primary generalized or segmental dystonia [87]. Forty patients were enrolled, and the posteroventrolateral portion of the GPi targeted. Following implantation, patients were randomly assigned into two groups that received either neurostimulation or sham stimulation. At the end of the 3-month blinded treatment phase, the neurostimulation group had an average of 39.3% reduction in motor symptoms as measured by the BFMDRS compared to the sham group, which had an average of only 4.9% reduction in motor symptoms. For the next 6 months, all patients received open label neurostimulation, at the end of which there was a 36.8% reduction in dystonia symptoms in the sham group, and continued benefit in the initial active arm. A post hoc analysis found a similar improvement in BFMDRS between the patients with generalized or segmental dystonia. At a 3-year follow-up of patients with primary generalized dystonia, the improvements noted at 1 year were sustained [88].

A long-term open label study of unilateral or bilateral GPi-DBs in 26 patients with DYT1 suggested that most in most patients the benefits of DBS are maintained over time [89]. At a mean follow-up of 6 years (range 3 to 10 years), the average worst scores on the BFMDS were significantly lower (and thus showed sustained improvement) compared to the original average pre-operative scores for both motor and disability components of the test ($P < 0.0001$). A meta-regression analysis found similar benefits in patients with DYT1 mutations. It identified 209 patients who had DBS for primary dystonia and found that those with the DYT1 mutation had the greatest percentage improvement (67.5%) while the overall mean percentage improvement of all patients with primary generalized dystonia was 60.7% [73].

Segmental Dystonia

Cervical dystonia has been successfully treated with GPi-DBS [89, 90]. A prospective, single-blind multicenter study of 10 patients with cervical dystonia who received bilateral GPi-DBS showed a significant improvement both pain and disability on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) from a mean 14.7 (higher scores indicating greater impairment) to a mean of 8.4 at 12 months post-surgery ($P = 0.003$) with improvements in both pain and disability [90]. A 10-year follow-up of GPi-DBS showed sustained improvement on the overall TWSTRS score of 68.1% [89].

The subthalamic nucleus (STN) has also been targeted and found successful in the treatment of cervical dystonia. A prospective study of nine patients with severe cervical dystonia at 12 months found an average of 62.9% improvement on the total TWSTRS score ($P < 0.001$) [78]. Five of the nine patients experienced depression, a known adverse effect of STN-DBS in Parkinson's disease, and interestingly, eight of the nine also had dyskinesias at some point during the programming process. Dyskinesias improved by lowering the stimulation voltage and then slowly increasing it, or by adding an additional dorsal contact without a change in voltage. No patient reported bradykinetic side effects.

Meige syndrome, which is the combination of oromandibular dystonia and blepharospasm, has also been successfully treated with DBS [91–98]. In a follow-up study of five patients treated with bilateral GPi-DBS, the mean movement and disability BFMDRS scores improved by 84% (range, 75–94%) and 89% (range 80–100%), respectively [91]. A long-term follow-up out to 78 months for bilateral GPi-DBS in Meige syndrome reported sustained benefit with a 53% improvement in the BFMDRS [93]. Studies suggest that bilateral stimulation is needed to adequately treat Meige syndrome [98].

Myoclonus dystonia has been successful treated with DBS. Although the ideal target is unknown, several case reports have found success with GPi [99–101], the ventral intermediate nucleus of thalamus (VIM) [79], or combined GPi-VIM target [102, 103]. A series of five genetically proven myoclonus dystonia patients

undergoing GPi-DBS found that median scores on the Unified Myoclonus Rating scale went from 76 points prior to surgery to 10 points at 6 to 9 months following surgery (less myoclonus with lower scores), and median BFMDRS scores went from an average of 30 points before surgery to 4.5 points after surgery [101]. In a patient who had genetically proven myoclonus dystonia with predominant myoclonus and tremor, VIM-DBS demonstrated moderate improvement in myoclonus, although it did not completely suppress the jerking [79]. A series of six patients with myoclonus dystonia who underwent bilateral VIM and GPi-DBS seemed to suggest that quadruple DBS may be slightly superior in comparison to either GPi or VIM-DBS alone [103]. These two small case series suggest DBS is of benefit to patients with myoclonus dystonia, but the ideal target or targets remain unknown.

There is only one case report describing DBS for rapid onset dystonia parkinsonism. The reported case was of a 23-year-old female who had bilateral GPi-DBs, which, unfortunately, did not improve the patient's condition [104].

Not all dystonic symptoms respond equally well to DBS, and studies suggest that there is less improvement in speech and swallowing symptoms than in other dystonic symptoms [84, 87, 105].

Secondary Dystonia

Patients with secondary dystonias are a highly heterogeneous population who typically have complex movement disorders that may include head injury, cerebral palsy and drug-induced, encephalitis-induced or post-anoxic induced motor impairments. Few studies have investigated DBS for this population, and when they have, the results have been mixed. A multicenter prospective study of GPi-DBS in 13 adults with dystonia-choreoathetosis cerebral palsy found a significant improvement in the BFMDRS motor score at 1 year post-surgery [106]. However, there was marked variability in the results, and four patients had no significant benefit. Due to the small sample size, it was not possible to identify factors that might predict outcomes.

A meta-analysis of 64 patients with cerebral palsy who underwent GPi-DBS found that there was a significant overall

improvement on the BFMDRS at 12 months post-surgery ($P < .001$) [107] with a negative correlation between the severity of the preoperative BFMDS motor score and the postoperative percentage improvement.

In a mixed group of patients with secondary dystonia due to cerebral palsy, drugs, post-encephalitis, or post-anoxic disorders, GPi-DBS resulted in mean improvements in BFMDRS motor and disability scores by 41.4% and 29.5% respectively [108]. However, four patients did not have any significant improvement in their BFMDRS scores.

In a small series of four patients with secondary hemidystonia due to focal traumatic brain injury there was a 73.2% improvement in BFMDRS motor scores and a 75% improvement in BFMDRS disability scores at 2 years post-unilateral GPi-DBS [109]. Other small case series of patients with traumatic injuries and post stroke injuries have reported mixed results. Some report improvement in BFMDS scores [110], while others note that patients report subjective gains despite the lack of symptom reduction as measured by the BFMDRS [111].

Complications

Unlike DBS for Parkinson's disease, GPi-DBS for dystonia does not appear to affect cognition or mood [112]. Most of the adverse effects of GPi-DBS for dystonia are related to the surgery itself and are similar to the surgical complications seen in DBS for other indications. Common reported complications include lead fracture, infection, cutaneous necrosis overlying a lead, and hematoma [84]. Infections are the most frequent complication and are typically addressed by temporary removal of the implanted system [87]. One study reported a mortality rate for GPi DBS of 0.4% and an intracranial hemorrhage rate of 2.2% [113].

Because the optic tracts lie ventral to the GPi, it is important that the electrodes are not inserted too deeply. Other possible adverse effects from incorrectly placed leads include tetanic muscle contractions, which can occur when the leads are positioned too far posterior or too medial to the target (Table 8.3).

Although GPi stimulation is considered relatively safe, recent publications have raised the possibility that using stimulation parameters effective for treating dystonia, may induce bradykinetic

parkinsonian symptoms in previously non-dystonic body regions, particularly gait slowing [80, 114]. One small study found that STN-DBS for cervical dystonia while effective caused temporary stimulation-induced dyskinetic movements that could be addressed by altering the stimulation parameters [78]. Other potential adverse effects of GPi stimulation include dysarthria and dysesthesia, although it is possible in most cases to alleviate these effects through stimulator programming manipulation.

Table 8.3 Electrode position relative to the GPi target and possible adverse effects

Location	Stimulation effect
Too Posterior	Tetanic muscle contractions
Too Anterior	No effects of stimulation
Too Lateral	No effects of stimulation
Too Medial	Tetanic muscle contractions
Too Superior	No effects of stimulation
Too Inferior	Visual phenomena evoked at low voltages

Sudden cessation of DBS for dystonia can occur if the neurostimulator battery dies or loses power. This can induce rapid reoccurrence of dystonic symptoms, and, particularly in patients with generalized dystonia, can translate into a medical emergency [115–117]. For this reason, ongoing monitoring of the neurostimulator battery and planned battery replacement is recommended.

SUMMARY

Dystonia is a complex, heterogeneous disorder that can have a major impact on patients’ lives. Despite the fact that few randomized, blinded trials of DBS for dystonia have been conducted, it is clear that some patients achieve significant clinical and functional improvements following GPi-DBS. The risks of surgery are relatively low, particularly in centers with experience in DBS. Careful screening of candidates is critical. There remains a need for further studies to help identify those patients who are most likely to benefit from DBS and to explore other targets within the basal ganglia that may be of therapeutic benefit.

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Chapter 9

Deep Brain Stimulation for Obsessive-Compulsive Disorder

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder that presents with constant or recurring intrusive, anxiety-generating thoughts known as obsessions, coupled with the initiation of repetitive behaviors or rituals, known as compulsions. Compulsions are perceived by patients with OCD as necessary to reduce anxiety [5]. There are several OCD-related disorders that are also characterized by obsessions and/or compulsions but should not be confused with OCD. These include among others, body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling disorder), and excoriation (skin-picking) disorder [5]. Both OCD and OCD-related disorders can be severely debilitating, interfering with social life, employment, and other activities of daily life. Today, OCD affects nearly 2% of the population in the United States. It is not gender-specific and it is often most severe in patients with co-morbid depression [8].

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According to the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-V) guidelines (2013), a diagnosis of OCD requires that a person have obsessions, compulsions, or both, as defined below. The symptoms must be time-consuming—that is, take up more than 1 hour per day—and they cannot be caused by chemical substances or other non-psychiatric medical conditions [5].

Obsessions

- (1) Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
- (2) The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

Compulsions

- (1) Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to internally driven rules that must be rigidly applied.
- (2) The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

Types of obsessions and compulsions vary from person to person; however, certain compulsions are observed in a majority of patients afflicted with OCD, such as excessive hand washing and fear that harm might come to themselves or a loved one if a specific compulsion is not performed. Compulsions can also consist of saying certain words or prayers in a specific order. Anxiety experienced by OCD patients is increased prior to carrying out a compulsion, but once carried out successfully, the patient's anxiety and fear can significantly decrease or abate entirely for a period of time.

NEUROPATHOLOGY

Because the ability to prevent intrusive thoughts and activities from interfering in daily life is thought to be impaired in OCD, it has been suggested that certain central neuronal circuits specifically involved in self-regulation and behavioral inhibition underlie this disorder [32]. One such system that consists of looped neural pathways that connect the thalamus to the cerebral cortex is the cortico-striato-thalamo-cortical circuit (CSTC). This system begins with excitatory glutamatergic projections from the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) to structures in the basal ganglia, including the internal capsule, nucleus accumbens (NAc), caudate, and putamen [12]. These structures, in turn, send projections to the thalamus which sends projections back to the same cortical structures from which the original signals originated [12].

It is thought that hyperactivity of various components of the CSTC circuit may be largely responsible for the characteristic obsessions and compulsions of OCD [12] (Fig. 9.1). In particular, the OFC and anterior cingulate cortex (ACC), the cortical components of the CSTC system, may play a role in OCD pathophysiology [28]. This concept is supported by findings in OCD patients showing hyperactivity in the lateral OFC, an area responsible for processing fear and negative thoughts, and in the ACC, an area responsible for reward anticipation, decision-making, empathy, impulse control, and emotion [28, 33]. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have confirmed hyperactivity in these cortical regions during both the resting and active state in OCD patients [2, 37]. Given these findings and that these brain structures are known to be important for reward and planning, it is possible that their dysregulation underlies some of the obsessive-compulsive symptoms of patients with OCD [10, 28].

Neurobiological findings from a number of sources have implicated genetic and immunological factors in the etiology of OCD, while the neurochemical basis of hyperactivity within the CSTC circuit remains presently unclear [31]. Some studies point to serotonin receptor down-regulation as potential factor for hyperactive behavior, while others have suggested that alterations

in extracellular tone in the caudate/putamen may result in downstream serotonergic regulation abnormalities that ultimately lead to hyperactivity within the CSTC circuit [26]. Other studies have found that the disruption of a variety of neurotransmitters, receptors, including neuropeptides along the CSTC circuit may be responsible for OCD symptoms [27]. Taken together, converging evidence from both basic and clinical research suggests that OCD neuropathology is complex, involving multiple neurotransmitter systems and both cortical and subcortical brain structures. Regardless, over the past 20 years there has been a concerted effort to treat the symptoms of OCD by modulating brain activity using pharmacological interventions, neurosurgery, or electrical stimulation.

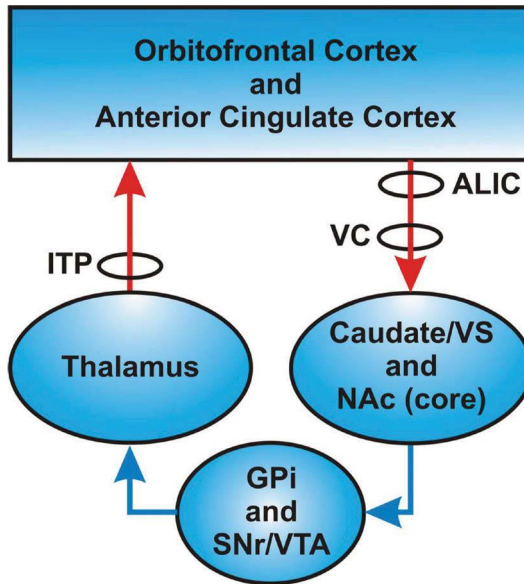


Figure 9.1 Basic diagram illustrating the components and pathways of the associative cortico-striato-thalamo-cortical loop. This circuit is thought to be hyperactive in OCD patients. Red arrows: excitatory glutamatergic projections; blue arrows: inhibitory GABAergic projections. (Abbreviations: Anterior limb of the internal capsule, ALIC; ventral limb of the internal capsule, VC; ventral striatum, VS; nucleus accumbens, NAc; globus pallidus interna, GPi; substantia nigra reticulata, SNr; ventral tegmental area, VTA; inferior thalamic peduncle, ITP.)

TREATMENT

In approximately 7.1% of patients analyzed in a prospective study, severely debilitating obsessions and compulsions persisted despite rigorous applications of pharmacologic and/or behavioral treatments, which included serotonin reuptake inhibitors, antipsychotics, and cognitive-behavioral therapy [27, 45]. As a result, there has been increased interest in the potential benefit of more invasive neurosurgical interventions for the subset of treatment-refractive patients.

The most widely used neurosurgical approaches for treatment-refractive OCD are capsulotomy and anterior cingulotomy, although subcaudate tractotomy and limbic leucotomy have also been applied [44]. Capsulotomy involves lesioning the ALIC, and anterior cingulotomy consists of lesioning the ACC. A study by Zhang et al. demonstrated a 35% reduction in obsessive and compulsive symptoms following bilateral capsulotomy and/or anterior cingulotomy performed in five out of the seven patients included in their study [44]. The connection between the ACC and the motor cortex via the rostral cingulate motor area, and its involvement in action selection (i.e., deciding what action to make), has led to the suggestion that alterations in neurochemical activity within these structures may be responsible for OCD symptoms [20]. However, while disconnection of these areas, via capsulotomy and anterior cingulotomy, has been shown to provide some relief, the overall therapeutic effectiveness appears only nominal, and both are highly invasive, irreversible, and do not provide benefit to all patients with treatment-refractive OCD [44]. For these reasons, other interventional approaches such as deep brain stimulation (DBS) have recently been explored.

DBS may be considered a promising, less invasive therapeutic option for OCD than neurosurgical interventions, in the sense that it does not entail a permanent and irreversible manipulation of the brain. While initial DBS surgeries focused on targeting the ventral aspect of ALIC, more recent studies have shown better outcomes with posterior placement of the electrodes in the bed nucleus of the stria terminalis (BST) [21]. These results have been instrumental in making DBS an FDA-approved therapy for treatment-refractive OCD in 2009. Since 1999 over 200 patients have received DBS for treatment-resistant OCD, and five different

targets have been tested [46]. They include the ALIC, ventral anterior limb of the internal capsule/ventral striatum (VC/VS), the NAc, the subthalamic nucleus, and the inferior thalamic peduncle [12].

DEEP BRAIN STIMULATION TARGETS

Anterior Limb of the Internal Capsule and the Ventral Capsule/Ventral Striatum

The first DBS surgical implantation procedures for OCD were conducted in 1998 at the Karolinska Hospital in Sweden where two patients underwent DBS of the ALIC with no apparent benefit [12]. Soon afterwards, however, other research groups began applying ALIC DBS in patients with OCD based on theories about the anatomic and functional importance of the structure in OCD dysfunction [12]. The ALIC is a structure of myelinated axons located between the caudate nucleus and the lenticular nucleus. It is an essential part of the CSTC because it transmits input from the subcortical nuclei, including the dorsomedial thalamus, and relays these signals to the cortex (see Fig. 9.1).

The ALIC as a viable DBS target was chosen for three fundamental reasons. First, the ALIC is necessary for thalamic and prefrontal cortical relay. Second, the ALIC interfaces with the BST, which, given its dense neuropeptides, neurotransmitter, and receptor composition, has been thought to play a role in OCD [27]. Oxytocin, vasopressin, opioid peptides are among the many neurochemicals present in the BST [27]. Third, the ALIC was the locus of many of the anterior capsulotomy procedures for OCD, of which 50–60% were successful. Thus, it was thought that the ALIC might be critical to OCD behaviors and that DBS of this region could better modulate symptoms than neurosurgical resection [12, 34].

The ALIC and VC/VS are in close proximity to one another. As a result, these structures can be stimulated either as a single target with a single DBS electrode and higher voltage (Fig. 9.2) or as individual targets with two different DBS electrodes and reduced voltage. Animal and human experiments as well as neuroimaging studies support the therapeutic effects of ALIC and VC/VS DBS. For example, MRI of patients having undergone ALIC DBS demonstrated a normalization of activity in the OFC after three months of stimulation [12]. These results suggest that

DBS of the ALIC is able to neutralize the hyperactivity in the orbitofrontal portion of the CSTC. The mechanism by which it exerts its effects is still elusive; however, it may be that DBS of the ALIC resets neurochemical release in both the medial OFC and lateral OFC, important in emotional regulation and fear processing respectively [12, 28, 33].

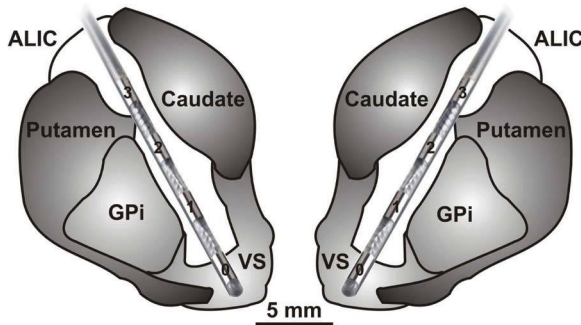


Figure 9.2 Bilateral targeting of the ALIC with DBS leads. 0, 1, 2, and 3 correspond to platinum/iridium stimulation rings. (Abbreviations: ALIC, anterior limb of the internal capsule; GPi, globus pallidus interna; VS, ventral striatum.)

Given the presence of CSTC fibers that project to and through the VC/VS, it is possible that DBS of the VS normalizes the hyperactive signal in these fibers and thus causes a normalization of symptoms. Additionally, because of the success of gamma knife capsulotomy procedures in the ventral parts of the ALIC in alleviating OCD, it was thought that perhaps DBS of the VC/VS might be more efficient in relieving symptoms than capsulotomy.

Therapeutic outcomes for these targets vary, but in general, the reported effects of ALIC and/or VC/VS shows it benefits in about half the patients treated. Among the earliest reported outcomes, Nuttin and colleagues found that based on clinical observation, three of their four patients benefited from bilateral ALIC DBS [36]. A study by Greenberg et al. showed positive outcomes in 16 of the 26 patients they studied [21]. A 2005 double blinded stimulation ON-OFF study by Abelson et al. found that two out of four patients benefited from ALIC stimulation [1].

Trials targeting the VC/VS show similar positive results. Tsai et al. found that in all patients undergoing DBS of this target, target stimulation induced smiling and laughter during surgery,

suggesting that DBS of this region may be responsible for mood and sensory changes [40, 47].

Nucleus Accumbens

The nucleus accumbens (NAc) has evolved as a significant target of DBS for a variety of psychiatric illnesses, including depression and OCD. Specifically, NAc DBS in rodents results in rapid increases in the release of dopamine and serotonin in the OFC. This may involve antidromic activation of corticofugal fibers passing through the NAc and projecting to mesocortical dopaminergic and serotonergic neurons in the ventral tegmental area (VTA) and raphe nucleus, respectively [43]. Its important role in reward and incentive-motivational behaviors make it a good choice for stimulation in patients with OCD.

Studies investigating the neurophysiological effects of NAc stimulation have found that 30 minutes of high frequency NAc stimulation in rats effectively inhibited the activity of nearly all orbitofrontal neurons via GABAergic mechanisms [41]. Moreover, neuroimaging studies in humans conducted by Figue et al. in 2011 demonstrated that patients with OCD exhibit increased activity in the NAc compared to healthy adults in a paradigm in which subjects were asked to conduct activities for monetary rewards [15].

To date, over 30 patients have been stimulated in the NAc with DBS. However, compared to DBS of the ALIC, NAc DBS has not been as consistently successful. While only 10% of patients responded to NAc DBS in a study conducted by Huff et al., 56% of patients showed improvement in a study conducted by Denys et al. [13, 23]. The wide variability in outcomes from NAc stimulation suggests that the surgical placement of NAc DBS electrodes may be a significant factor in patient outcomes. It is possible that the area of dysfunction in OCD is localized to a specific part of the NAc/VS complex and that more precise targeting is needed to assess the true efficacy of DBS stimulation in this region.

Subthalamic Nucleus

Interestingly, the subthalamic nucleus (STN) has also been considered as a target for OCD, particularly for individuals with comorbid movement disorders [16]. In fact, this target

was discovered after DBS surgery of a patient with Parkinson's disease who also happened to have OCD symptoms. Not only was the patient resolved of his motor symptoms associated with PD but also of his OCD [16]. The STN is located dorsally to the substantia nigra (SN) and projects to the thalamus via the STN hyperdirect pathway, making it part of the CSTC pathway. One hypothesis of the therapeutic effect of STN DBS for OCD stems from the idea that it leads to the release of adenosine from astrocytes in the thalamus, which in turn can reduce excitatory transmission in the thalamus [6]. Mitigation of excitatory transmission in the thalamus may, in turn, normalize the hyperactive state of the CSTC circuit in OCD patients, leading to symptom relief. Animal studies have further supported the efficacy of STN stimulation for OCD. For example, Benazzouz et al. found that high-frequency stimulation of the anterior STN significantly mitigated repetitive behaviors in non-human primates [7].

A 2008 multicenter study of 17 patients in which 14 patients had bilateral STN DBS and two had unilateral STN DBS showed a mean decrease of 41% in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) baseline score after three months of active stimulation [30] (lower scores on the Y-BOCS indicate improvement). However, the number of OCD patients that have been stimulated with STN DBS is low compared to those targeted in the ALIC [9], thus further studies are necessary to confirm whether or not STN DBS is comparatively more effective in treating OCD.

Inferior Thalamic Peduncle

DBS of the inferior thalamic peduncle (ITP) has also been conducted for OCD management [25]. It is perhaps the unique location of the ITP, connecting the thalamus to the OFC, which enables the ITP to mediate ameliorative effects [25]. In addition, the ITP has been shown to play an important role in the inhibition of irrelevant stimuli [12, 25], and thus its stimulation may help reduce the intrusive thoughts (i.e., irrelevant stimuli) that characterize OCD [5]. In addition, PET studies have shown that the ITP and the OFC are hyperactive in depression as well as in OCD. Thus, the ITP may be a beneficial target for patients who have OCD and are co-morbid with depression [25]. Jimenez-Ponce et al. have shown that five of five patients stimulated in the ITP exhibited a

significant decrease in their Y-BOCS scores, suggesting that the ITP as a DBS target for treating OCD warrants further investigation.

Globus Pallidus Interna

The globus pallidus interna (GPi) has been suggested as a DBS target for patients with OCD and co-morbid Tourette syndrome [35]. The GPi is known to send inhibitory projections to the thalamus (Fig. 9.1) [35]. Thus, it is possible that GPi dysfunction may lead to hyperactivity of the thalamus and the CSTC circuit, resulting in OCD obsessions and compulsions. In support of this target for the treatment of OCD, high-frequency stimulation of the rodent GPi has been shown to result in a significant reduction in OCD-like behaviors [14]. In a patient case study, Rodrigo et al. found that GPi infarction caused by carbon monoxide poisoning led to OCD symptoms in one patient [38]. In a study of nine patients with GPi DBS, who also exhibited Tourette syndrome, Cannon et al. found a significant reduction in the Y-BOCS score (a mean 59% decrease in baseline scores) in 78% of patients [11]. Lastly, a recent study of four additional patients with severe OCD who were implanted in the GPi showed a significant decrease in obsessions and compulsions as assessed by the Yale Global Tic Severity Scale (YGTSS) and Obsessive-Compulsive Inventory (OCI) tests [35].

THERAPEUTIC OUTCOMES

There are several ways to measure DBS therapeutic outcomes for OCD. Earlier studies relied on clinical observations, while more recent studies have used standardized measures, such as the Y-BOCS in which the higher the score, the more severe the symptoms, the YGTSS, which is most commonly used in patients with combined dystonia and OCD, and the OCI [19]. Although adverse effects and complications are not uncommon in OCD patients treated with DBS, they can usually be controlled by adjusting stimulation parameters. In addition, increased experience in the application of DBS for psychiatric illnesses should help to inform more accurate targeting of brain structures and the reduction of unwanted adverse effects of OCD treatment [9]. Outcomes of patients who underwent DBS implantation in any of the five

targets discussed above have been found to produce significant symptom relief, some more effective than others (Table 9.1).

Table 9.1 Case studies and clinical trials of patients undergoing DBS for OCD with outcomes from 2000-present

DBS lead location	Study conducted	Year	Patient #	%Success (# of patients with Y-BOCS score change $\geq 35\%$ / Total # of patients $\times 100$)	Time to follow-up (months)
ALIC	Nuttin et al. [36]	1999	4	75 (clinical observation)	N/A
	Anderson et al. [3]	2003	1	100	10
	Abelson et al. [1]	2005	4	50	4–23
	Greenberg et al. [21]	2010	26	62	3–36
	Van den Munckhof et al. [42]	2013	9	100	2
VC/VS	Greenberg et al. [22]	2006	10	40	36
	Goodman et al. [18]	2010	6	67	12
	Tsai et al. [40]	2014	4	50	15
NAc	Sturm et al. [39]	2003	5	60	24–30
	Aouizerate et al. [4]	2004	1	100	27
	Franzini et al. [17]	2010	2	50	24–27
	Huff et al. [23]	2010	10	10	12
	Denys et al. [13]	2010	16	56	21
STN	Mallet et al. [29]	2002	2	100	6
	Fontaine et al. [16]	2004	1	100	12
ITP	Jimenez-Ponce et al. [24]	2009	5	100	12
GPi	Cannon et al. [11]	2012	9	78	4–30
	Nair et al. [35]	2014	4	100 (YGTSS and OCI scores)	3–26

Source: Adapted from Blomstedt et al. [9].

Abbreviations: Anterior limb of the internal capsule, ALIC; ventral capsule/ventral striatum (ventral olfactory tubercle, ventral caudate and putamen, including the nucleus accumbens), VC/VS; nucleus accumbens, NAc; subthalamic nucleus, STN; inferior thalamic peduncle, ITP; globus pallidus interna, GPi.

None of the above targets are consistently able to provide relief in 100% of patients. This may be due in part to inconsistencies in the surgical procedure across institutions and among surgeons. It may also be that the actual therapeutic target is located just slightly away from the sites currently targeted. Each of the studies cited here used relatively high voltage stimulation, which may lead to current spread and thus potentially stimulate neighboring brain regions [12].

Complications

As with any surgical procedure, there are risks associated with DBS surgery. Perhaps the most significant of these complications are infection/hemorrhage, unwanted stimulation side-effects, or electrode-related problems. Of the procedure-related complications, intracerebral hemorrhage was found to occur in 7.7% of 26 total patients implanted for OCD in a single study conducted by Greenberg et al. [21]. This number is greater than the number of complications seen in DBS for movement disorders, and it has been suggested that it may be related to the relative inexperience of surgeons in conducting DBS for OCD, compared to DBS for movement disorders [9]. Moreover, the proximity of these targets to the vascular supply, including bridging veins, may also be a factor in increased rates of intracerebral hemorrhage occurrence with OCD DBS [21].

Other therapy related complications include anxiety, sadness, euphoria, as well as hypomania or mania [12]. However, these symptoms are usually reversible with voltage adjustments. Cognition has not been affected in any of the published cases to date.

SUMMARY

Ultimately, as the studies reviewed here indicate, DBS holds great promise as an effective intervention for patients suffering from treatment-refractive OCD. Although there is as yet no definitive consensus on the optimal targets, continued research and clinical trials will help identify the targets of choice. As is true of DBS for other applications, the precise mechanisms of its therapeutic benefit for OCD remain unknown. Further research coupled

with neuroimaging studies of the neuromodulatory effects of DBS will help improve understanding of the neuropathology of OCD and the local and distal effects of DBS for this psychiatric condition.

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Chapter 10

Deep Brain Stimulation for Tourette's Syndrome

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INTRODUCTION

First described by the French physician, Georges Gilles de la Tourette, who published his findings on nine patients in 1885 [2], Tourette's syndrome (TS) has been studied for over a century. Today, it is considered a neurodevelopmental disorder characterized by the presence of multiple, chronic motor tics and one or more vocal/phonic tics, often associated with behavioral comorbidities [3]. Although the symptoms commonly abate before age 18, a subset of patients remains symptomatic into adulthood. While once considered rare, recent community epidemiologic studies involving direct examination of subjects indicate that 1–3% of school children have TS [5, 6]. Non-invasive therapeutic approaches include psychotherapy and pharmacotherapy. In 1999, deep brain stimulation (DBS) emerged as a new therapeutic option for patients with severe TS refractory

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to traditional therapies; since then, over 100 patients have been treated with DBS (for a detailed review see Schrock et al., 2015 [1]).

Symptom Characteristics

Tics associated with TS take several forms. Motor tics are abrupt, involuntary, repetitive movements. They are categorized as “simple” when they involve a single movement, such as head jerking or eye blinking, or as “complex,” when they involve combinations of movements that simulate purposeful actions, such as neck twisting plus facial grimacing. Phonic tics are simple, involuntary sounds such as grunting, snorting, or barking. Verbal tics consist of single words or word phrases which can take the form of coprolalia (vocalization of socially inappropriate words), echolalia (repetition of the words or phrases of others), and palilalia (repetition of one's own words or phrases). Although tics are the defining symptom, up to 90% of patients with TS are also affected by comorbid psychopathologies, including obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) [4].

Despite intense effort from clinicians and researchers, the underlying pathophysiology of TS remains uncertain. Although there are competing hypotheses, it is generally agreed that the manifestations of TS are associated with abnormalities in the cortico-basal ganglia-thalamo-cortical circuits (CBTC) and may be a consequence of dysfunctional dopaminergic or GABAergic networks [7–10]. It has been postulated that an overactive thalamocortical system is responsible for TS deficits. However, the exact location of dysfunction within the CBTC pathways remains unclear [11, 12].

Available Therapies

The need for treatment is highly variable and depends on disease severity, related impairment, and temporal course. For some individuals, tics are mild and do not require treatment. For many others, tics can interfere with the normal flow of motor activities and cause mild to severe pain, embarrassment, and social isolation. The natural history of the condition is such that over time, particularly in late adolescence and early adulthood, tics tend

to lessen in severity [13]. However, in about one-third of cases, tics persist throughout life and can become disabling [14].

A variety of medications are available to treat TS, including alpha agonists, classical neuroleptic antipsychotics, and the newer atypical antipsychotic medications, as well as behavioral therapies [15]. While many patients benefit from pharmacotherapy, the medications may produce an inadequate response and are often poorly tolerated due to common or severe adverse effects, which can include depression, weight gain, feeling sedated, and extrapyramidal side-effects.

A small percentage of patients have symptoms that are intractable to any of these noninvasive, traditional treatments [16]. As a result, since the 1950s neurosurgical procedures have been attempted to manage patients with refractory symptoms. Among the first of these surgeries was frontal leucotomy, a procedure with few if any positive effects. Since then, targeted ablation surgery has been conducted in approximately 65 patients worldwide. Structures targeted for lesioning included the subthalamic nucleus, the cingulate, other loci in the limbic system, and even the dentate nucleus [15]. Although most case studies have not included validated outcome measures nor blinded ratings, the results have been reported as generally inadequate in symptom improvement or as poorly tolerated with potential major complications, including hemiplegia, cognitive impairment, dysarthria, dysphagia, akinesia, and gait disturbances [17].

DEEP BRAIN STIMULATION FOR TOURETTE'S SYNDROME

With the advantage of safety, reversibility and adjustability, DBS has largely replaced ablation surgery for neurological movement disorders like Parkinson's disease, tremor, and dystonia. Since the introduction of DBS for TS, nine brain regions have been chosen as stimulation targets, including: (1) the centromedian parafascicular complex (CM-Pf); (2) the substantia periventricularis and nucleus ventro-oralis of thalamus; (3) the anteromedial and ventro-posterolateral areas of the internal segment of the globus pallidus (GPi); (4) the external segment of the globus pallidus (GPe); (5) the dorso-medial nucleus of thalamus; (6) the subthalamic

nucleus; (7) the ventral striatum/nucleus accumbens (NAc); (8) the anterior limb of the internal capsule (ALIC) [1].

In published case reports of DBS for TS, the change in tic scores varies between a 17% deterioration to a 90% improvement. Given the small number of patients treated to date, DBS for TS remains experimental. The definitive target has yet to be determined and will most likely need to be tailored to each patient's symptom complex. The current targets of choice include the CM-Pf, the GPi, and the internal capsule/NAc [19–23].

DBS TARGETS

Centromedian-Parafascicular Complex

Based on successful tic control using stereotactic ablation of the CM-Pf by Hassler and Dieckmann in the 1970s [24], Visser-Vandewalle and colleagues introduced Vo/CM-Pf DBS for TS in 1999 [18]. They targeted the cross point between the centromedian (CM) and ventral oral (Vo) internal thalamic nuclei and substantia periventricularis in three patients, who then experienced a 72% to 93% reduction in tics at a follow-up of 1 to 10 years [24, 25]. Although not assessed quantitatively, the comorbid compulsions and the self-harming behavior present in one patient resolved completely [24].

Several years later, the same group targeted the CM-Pf complex in a randomized, controlled stimulus ON-OFF trial of six patients [26]. They observed a significant reduction of 37% in tics in the stimulation ON phase compared to the stimulation OFF phase as assessed by the Yale Global Tic Severity Scale (YGTSS) [27], a widely used clinical tool to assess TS severity. The total score on the YGTSS can be divided in three subscores addressing motor tics, phonic tics, and disease-associated impairment level, with lower scores indicating decreased symptom severity. At one-year follow-up, the average YGTSS score was reduced by 49% compared to preoperative scores, and the modified Rush Video-Based Tic Rating Scale (mRVRS), which uses video recordings to count phonic and motor tics [28], showed a 35% tic reduction.

In 2013, Okun et al. [29] conducted a randomized, controlled trial of scheduled (intermittent) CM-Pf stimulation in five subjects with TS. At the 6-month follow-up, they, too, found a statistically

significant reduction in the YGTSS total, impairment, and motor scores, and in the mRVRS phonic and total scores.

The efficacy of CM-Pf versus anteromedial pallidum stimulation was compared in three patients undergoing a cross-over trial of sham, CM-Pf, and pallidal stimulation with a follow-up of 20–60 months [30–32]. Pallidal stimulation reduced tic severity assessed by the YGTSS by 65%, 96%, and 74% in patients 1, 2, and 3 respectively, while CM-Pf stimulation reduced tic severity by 64%, 30%, and 40% respectively. No further reduction in tic severity was reported when both targets were stimulated simultaneously. Depressive mood, emotional hypersensitivity, moderate anxiety, and impulsivity tended to decrease with CM-Pf or simultaneous CM-Pf and pallidal stimulation, but not with pallidal stimulation alone [22].

In a prospective, randomized, double-blind crossover trial of five adults with TS, Maciunas et al. [33] reported the superiority of bilateral CM-Pf DBS over unilateral and sham stimulation in reducing tic frequency and severity with significant reduction in motor and phonic tics as measured by the YGTSS. However, after three months of unblinded stimulator programming, only 3 out of 5 patients achieved more than 50% benefit.

In 2010, Servello et al. presented the largest case series of Vo/CM-Pf DBS for TS to date. Thirty-four patients underwent bilateral thalamic stimulation, with both long- and short-term follow-up showing significant reduction in tic and comorbidity scales [34]. The YGTSS scores of the 19 patients that reached a 2-year follow-up went from a preoperative average of 76.9 points to 36.7.

Reported stimulation-related adverse effects of CM-Pf DBS for TS include paresthesias, dizziness, asthenia, lethargy, eye movement and visual disturbances, altered sexual function, nausea, and anxiety [22, 25, 26, 29, 32, 34]. Ackermans et al. reported the occurrence of persistent vertical gaze palsy due to mesencephalic hemorrhage at the tip of one electrode [35]. One episode of acute psychosis was reported following implantation [33].

Globus Pallidus

A smaller number of patients have undergone GPi DBS for TS. The posterolateral-ventral (sensorimotor) GPi, the main basal ganglia

output to the thalamus and cortex, has been targeted in most cases, although the anteromedial (limbic) GPi has been adopted in a few. The first report of DBS of the posterolateral-ventral GPi was by the same Dutch-Belgian [18, 36] group who conducted the first trial of CM-Pf DBS for TS. They targeted the medial thalamus (MT) and GPi in a single patient and found that bilateral MT stimulation reduced tics by 80% at high stimulus intensities, and GPi stimulation reduced tics by 95% at low stimulus intensities. Subsequent reports in the literature support GPi DBS in tic reduction, with no benefit for comorbidities [37, 38].

CONNECTIONS AND POSSIBLE MECHANISM OF CENTROMEDIAN-PARAFASCICULAR DBS

TS symptoms span neural functions likely controlled by sensorimotor, associative, and limbic regions of the brain, many of which have been implicated in TS pathophysiology. The CM-Pf complex, located among the intralaminar nuclei of the thalamus, sends a dense excitatory output to the striatum. Non-human primate studies support a functional differentiation between the CM and the Pf nuclei. Anterograde axonal tracing showed CM projections to sensorimotor areas (post-commissural putamen), and Pf outputs to the associative striatum (caudate and rostral putamen) [39–41].

It has been suggested that the CM receives input from the motor cortex, reticular formation, cerebellum, vestibular nuclei, superior colliculus, pretectum, and locus coeruleus, [42] and sends projections to the motor loop from the medial CM nucleus to the post-commissural putamen, from there to the ventrolateral GPi, and back to the CM [43], and that it has a much smaller projection to the primary motor cortex [44]. The effect of CM projections to the striatum is complex, and likely due to local processing of thalamic inputs by striatal interneurons with resultant excitation or inhibition of striatal activity upon CM stimulation [45–47].

The Pf receives inputs from associative frontal, temporal, parietal, and occipital cortices, and projects to the premotor, prefrontal, and anterior cingulate cortices [48–50]. Striatal interneurons significantly modulate the effect of projections from the Pf. Recent studies suggest that such inputs target cholinergic

and GABAergic neurons, with activation of the Pf, which results in a GABA-mediated inhibition of striatal acetylcholine release [51–54].

Despite the present knowledge about these connections, the mechanisms and the networks modulated by DBS in TS are not fully understood. A recent large animal fMRI study identified certain distinctive network modulatory effects of CM-Pf stimulation [55]. Structural neuroimaging studies in patients with TS suggest that reduced cortical thickness in motor, premotor, prefrontal, and lateral orbito-frontal cortical areas may be correlated with clinical expression of symptoms [56], including simple [57, 58] and complex tics, [56] and psychiatric comorbidities [59, 60]. An fMRI study correlated tic generation with neural activation in the motor pathway, including the sensorimotor cortex, pallidum, substantia nigra, and putamen [61]. Other neuroimaging studies have found structural changes in the basal ganglia, prefrontal cortex, and other portions of the limbic system. Amygdala hypersensitivity has also been observed in TS in response to emotional facial expressions [62]. Functional disorganization of cortico-basal ganglia networks and abnormalities in associative limbic networks (i.e., orbito-frontal and prefrontal dorsolateral cortices) have been reported [63].

Individual characteristics of tics have been correlated with varying regions of the brain. Severity, for example, has been correlated with the degree of abnormality in the premotor, sensorimotor, parietal and cingulate cortices, and in the medial thalamus, while tic complexity and premonitory urges, are associated with abnormalities in sensorimotor areas and associative/limbic networks [63, 64].

Due to the complexity of TS pathophysiology and its manifestation, and in order to further investigate the link between circuitry effects of DBS and behavioral outcomes, an accurate disease animal model is necessary. Worbe and McCairn et al. have proposed steps towards a primate model of TS, in which GABA-antagonist injections in the striatum result in TS-like symptoms [65–67]. This model has shown that tic-like movements were associated with activity in the sensorimotor network and hyperactivity in the associative regions of the brain, and that stereotypic behaviors were linked to activity in the orbitofrontal cortex and in the limbic basal ganglia.

SUMMARY

TS is a neuropsychiatric disorder consisting of motor and vocal tics, ranging from mild to severe and debilitating, which are often accompanied by behavioral comorbidities. Given its success in treating other motor-based disorders such as Parkinson's disease, DBS may become an alternative therapy for severe TS. The wide variety of symptoms in TS, which are attributed to numerous brain regions, have so far made it difficult to determine the optimal target for this heterogeneous disorder. However, the CM-Pf complex is proving to be a target of interest. By inhibiting areas of the brain that are considered as contributing to impaired sensory motor and emotional processing in TS patients, DBS of the CM-Pf may alleviate more TS symptoms than other targets. CM-Pf stimulation has also been shown to modulate networks that contain projections from the thalamus to the striatum, and the majority of thalamostriatal projections originate within the CM-Pf.

Although clinical reports show DBS can provide some benefit for TS, the variability among patients and their symptoms and the small patient numbers in most studies to date prevent the generalization of research findings to standard clinical practice. Large randomized, double-blinded, controlled studies are necessary to establish efficacy and safety of TS DBS and the most beneficial target for controlling tics and comorbidities. Further understanding of network effects of corticostriatal and thalamostriatal projections, as well as the modulatory effects of GABAergic systems may add to our understanding of the mechanisms of both TS and DBS for TS and thus advance research and clinical application of DBS for patients with this disorder.

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Chapter 11

Deep Brain Stimulation for Treatment-Resistant Depression

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INTRODUCTION

Deep brain stimulation (DBS) has emerged as an alternative, reversible, nonablative neuromodulatory treatment for severely refractory major depressive disorder (MDD) and bipolar depression (BD). In the past decade, DBS for mood disorders has been reported in small case series, and it remains largely investigational. For those patients who do not receive therapeutic benefit from other available treatment options, including pharmacotherapy, psychotherapy, and electroconvulsive therapy, DBS holds promise [1, 2]. In general, DBS is believed to work by modulating the cortico-striato-thalamo-cortical (CSTC) circuits (see Fig. 11.1). The CSTC and its associative limbic and motor circuits have been implicated in the pathogenesis of MDD and BD. Various DBS targets have been examined for treatment-resistant depression

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(TRD) including the subgenual cingulate gyrus, ventral capsule/ventral striatum, nucleus accumbens, inferior thalamic peduncle, lateral habenula and the medial forebrain bundle. Still, many important clinical questions remain, including: (1) what is the most appropriate, effective and therapeutically consistent target, (2) what are the optimal stimulation parameters, and (3) what are the progressive mechanisms of action and how can recovery be optimized over time? This chapter will review reported clinical trials of DBS for MDD and BD, describing rationale for target selection, reported efficacy, clinical applicability and hypothesized mechanisms of action.

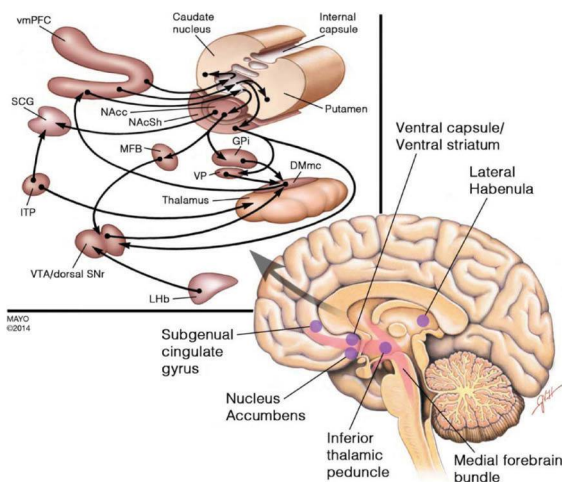


Figure 11.1 Various DBS targets and modulation of the CSTC circuits. *Abbreviations:* vmPFC, ventromedial prefrontal cortex; SCG, subcallosal cingulate gyrus; ITP, inferior thalamic peduncle; VTA, ventral tegmental area; dorsal SNR, dorsal substantia nigra pars reticulata; LHb, lateral habenula; VP, ventral pallidum; DMmc, dorsomedial motor cortex; GPI, globus pallidus; MFB, medial forebrain bundle; NAcc, nucleus accumbens core; NAcsh, nucleus accumbens shell.

DBS TARGETS AND OUTCOMES

Subcallosal Cingulate Gyrus

To date, the subcallosal cingulate gyrus (SCG) is the most extensively researched DBS target for TRD. Reversal of SCG

hypermetabolism in TRD is the primary rationale for targeting this region with high-frequency stimulation DBS [3–6]. Clinical trials of SCG stimulation were originally described in 2005 by Helen Mayberg and colleagues in a trial of 6 patients and subsequently in a larger study of 20 patients [4]. Approximately two thirds of patients in these studies showed improvement of MDD symptoms, and 35% had complete remission. Blinded, sequential intraoperative stimulation at 130 Hz was applied to determine the threshold for safe and effective stimulation. At final follow-up (three to six years), 42.9% of patients demonstrated complete resolution of symptoms [7].

In an effort to replicate and extend these findings, Puigdemont et al. [8] investigated the short and long-term outcomes and safety of SCG in an independent sample of six patients. Response rates in this group were similar or greater than those reported previously. Seven patients displayed marked improvement after six months of chronic stimulation, and 50% remitted after one year of DBS. During the follow-ups, antidepressant drugs were not changed but were reduced in parallel with signs of clinical improvement. Interestingly, Puigdemont et al. [8] found a significant relationship between long-term response and electrode location. Another earlier study, analyzing responders versus nonresponders in SCG DBS, found robust white matter tract connections from the SCG target to the orbitofrontal cortex, amygdala/hippocampus, hypothalamus, and NAcc to be critical for mediating therapeutic effects of DBS [9]. Riva-Posse et al. [10] further defined the combination and location of specific white matter tracts necessary to achieve clinical response. Tractography maps revealed a fiber bundle template involving bilateral forceps minor, cingulum, and medial frontal striatal/subcortical fibers activation was responsible for response and remission.

More recently, Holtzheimer et al. [11] presented an open-label, sham-stimulation study of 17 patients with treatment-resistant unipolar and bipolar depression undergoing DBS of the SCG. In this single-center study, the majority of patients (92%) responded, and over a half (58%) were in remission following two years of stimulation. However, for some patients, improvements in depression severity took longer to emerge without any clear reasons for the delay. It seems likely that premorbid functioning, psychosocial support and temperament/personality contribute

to the rate of recovery and responsiveness in patients with TRD. Overall these findings argue against a clinically significant sham effect over time. Although depression severity was significantly lower after four weeks of sham stimulation, the mean reduction was not clinically significant.

SCG DBS may work by normalizing CSTC neural networks through a reduction of SCG activity. Given the strong reciprocal connectivity between the prefrontal cortex and brainstem monoaminergic nuclei, SCG DBS may normalize a putative monoaminergic hypofunction secondary to abnormal inputs from the prefrontal cortex [8].

Ventral Capsule/Ventral Striatum

Stimulation of the ventral capsule/ventral striatum (VC/VS) was first performed in patients with Obsessive Compulsive Disorder (OCD), and it was found that not only were there improvements in OCD symptoms but also in depression scales. These findings led to the exploration of the VC/VS as a TRD [10, 11]. Greenberg et al. [11] reported that 50% of the eight OCD patients with comorbid depression experienced improved mood and affect. These observations, together with their involvement of CSTC circuits, opened up further clinical trials and preclinical investigations targeting VC/VS for the treatment of severe MDD patients.

In 15 patients with VC/VS stimulation, Malone et al. [12] found that patients demonstrated a 20% remission rate after six months of treatment and a 40% responder rate at the last follow-up as measured by the Hamilton Depression Rating Scale (HDRS). Remission rates as assessed by Montgomery-Asberg Depression Rating Scale (MADRS) were 33.3% at three months, 26.6% at six months, and 33.3% at last observation. DBS was reported to be well tolerated, with minimal complications. Most notable complications included pain at implantation site, lead fracture, transient hypomania, increased depression, transient dysphagia, and syncopal episodes [12]. Hypomania was resolved by adjusting the stimulation parameters. One incident of worsening depression was addressed by changes in medication and a close monitoring of neurostimulator battery function. The authors stressed the

importance of postoperative care given the return of depressive symptoms after accidental battery depletion or failure. Relative to cognitive functioning, Kubu and colleagues [13] observed no decline across individuals, and neuropsychological improvements were reported in 10 OCD and 11 MDD patients. Similarly, Malone et al. [14] failed to find deleterious effects on measures of general intellectual ability, language, processing speed, executive function, learning and memory.

Taken together, the reported clinical findings VC/VS as a target for DBS provide encouraging evidence of sustained therapeutic effects. With close postoperative monitoring and successful electrode implantation, this region offers therapeutic potential for individuals suffering TRD who are unresponsive to conventional treatments.

Nucleus Accumbens

The reward circuitry of the nucleus accumbens (NAc) has been associated with depression for many years. The NAc is located within the most ventromedial portion of the VS. Considering its intimate connections to areas involved in depression phenotypes, the NAc emerged as a potential target for DBS.

Schlaepfer et al. [16] found that in an initial study of three patients undergoing DBS of the NAcc improvements occurred in anhedonia (i.e., inability to feel pleasure but the patients did not experience complete remission. The changes brought about were reflective of positive affect and metabolic changes in brain networks associated with depression. After one week of DBS, it was found that metabolic activity increased in the NAc, amygdala, and the dorsolateral and dorsomedial prefrontal cortex and decreased in the ventral and ventrolateral medial prefrontal cortex, which have been described as hypermetabolic in depressed states). These observations support the hypothesis that NAc DBS can modulate the CSTC circuit.

Preliminary positive effects of NAc DBS on depression were thus established, yet there was limited information about its impact on cognitive functioning. At one year after bilateral NAcc DBS, Grubert et al. [17] found no cognitive decline and a trend towards improved cognitive performance, generally improving

from below average to average performance in 10 patients. These precognitive effects were independent of the antidepressant effects or changes in NAcc DBS parameters.

Recently, a larger-scale study by Bewernick et al. [1] reported that 5 of 11 (45%) patients responded, and the treatment effect seen at 12 months was sustained at four years. Ratings of both depression (HDRS, MARSD) and anxiety (Hamilton Anxiety Scale) were significantly reduced from the first month of DBS on. Equally important, improved hedonic activities were also reported in those responders. Notably, all 11 patients improved on quality of life measures. However, one nonresponder committed suicide, which the authors judged to be unrelated to the DBS. Other than this adverse event, the only adverse effects were weak symptoms of hypomania (elevated mood, fewer hours of sleep), which were observed in two patients after a stimulation parameter change and which disappeared within 24 hours.

In patients who responded well to NAcc DBS, the effects have been sustained and have not adversely affected cognitive function. As it is true for other DBS sites, there is surgical risk of the procedure itself. However, given the role of the NAcc in reward, motivation, aggression and impulsivity, there are also psychiatric risks in targeting the NAcc, including the possibility of aggravating depression or generating other adverse effects such as mania and suicide.

Inferior Thalamic Peduncle

The inferior thalamic peduncle (ITP) is a system of fibers that connect the midline and intralaminar thalamic nuclei of the nonspecific thalamic system (NSTS) with the orbitofrontal cortex, which is involved in the physiopathology of MDD. Subcortical orbitofrontal cortex (OFC) connections include the temporal lobe amygdala, ventral striatum, hypothalamus, substantia nigra, raphe nuclei and ventral tegmental area. The physiological and anatomical significance, together with postmortem imaging observations highlight ITP and its related circuits as engaged in mood and behavior control [18].

The first and only report of targeting the ITP was a 2005 case study by Jimenez et al. of a 49-year-old patient with recurrent

episodes of unipolar depression of 20-year duration. Eight contact stimulating electrodes were bilaterally implanted in areas at and around the ITP. Continued electrical stimulation improved depression as measured by the HDRS without antidepressant medication [18].

Preclinical experiments of the effects of DBS on the ITP present particular challenges. The ITP is not identified in the rat stereotactic atlas, thus lesions and electrical stimulation of the reticular thalamic nucleus and OFC (structures connected by the ITP) have been used as an alternative. This may explain the lack of preclinical and clinical research on the ITP DBS for TRD. However, the ITP remains an interesting exploratory target. Previously mentioned DBS sites in this chapter as well as regions implicated in MDD (e.g., temporal lobe amygdala, hypothalamus) all have anatomical connections with the OFC. Moreover, the anatomical proximity of the internal capsule, the NAc and the ITP opens up the possibility that the stimulated area may involve more than one target.

Lateral Habenula

Studies have reported increased activation of the lateral habenula (LHb) in humans with depression [19, 20] as well as in certain animal models of depression [21, 22]. Increased activation of this region leads to the down regulation of the serotonergic, noradrenergic, dopaminergic systems and stimulation of the hypothalamic–pituitary axis.

Recently, LHb DBS has yielded successful results and is thought to be a mediating mechanism for antidepressive actions [23, 24]. One patient showed initial symptom remission, but experienced two full relapses when the stimulation device malfunctioned, although the patient was unaware of the malfunction [24]. The second improved more than 50% as measured by the Hamilton Depression Scale, but suffered from a comparable relapse during an off period when the stimulation device was changed following infection.

Strikingly, the DBS-OFF relapses in the abovementioned cases were rapid in onset, occurring approximately within one week, and the remission times were slow, taking over 8–12 weeks to occur in the DBS-ON phase. Similar patterns were also

noticeable in patients treated with DBS of the SCG. Of note, the SCG as well as the medial forebrain bundle is part of the midline neurocircuitry that potentially affects the LHb inhibitory projections. For this reason, the investigators suggest that the uneven time course observed in those two patients (e.g., rapid relapses followed by slow remissions) is likely linked to alterations of neuroplasticity and perturbations of monoaminergic systems that are pertinent to theories of depression [24].

One of the major surgical challenges of DBS in this area is the prevention of intracranial bleeding when introducing the electrode. Careful and precise anatomical planning is required. Schneider and colleagues [25] recently conducted a feasibility and safety study of LHb DBS in 27 patients. They found that a standard frontal trajectory ($>40^\circ$ relative to anterior commissure) was safe for bilateral stimulation in 48% of the patients and that a steeper frontal trajectory (that is $<40^\circ$ relative to the anterior commissure) was required for bilateral stimulation in 96% of the cases. They concluded that DBS of this small midline structure or rather, its major afferent bundle which is adjacent to the third ventricle and thalamus related vessels, presents predictable, but solvable challenges to neurosurgeons [25].

Medial Forebrain Bundle

In 2013, Schlaepfer et al. explored supero-lateral branch of the medial forebrain bundle (slMFB) DBS in a pilot study of six patients. The modulation of a network of forebrain structures via the MFB was inadvertently discovered by activation of myelinated fibers descending from the frontal lobe into the ventral tegmentum area (VTA). It was thought that upstream dysfunctional cortical input into the network might thus be ameliorated by modulating cortical regions, whereas downstream dopaminergic VTA neurons could be recruited and activated directly. As a result, the VTA might exert its activating effects on forebrain structures and the prefrontal cortex by way of DBS to the slMFB.

A pilot study on the safety and efficacy of slMFB DBS in seven patients with TRD showed that all seven had similar intraoperative effects of increased appetitive motivation [26]. At last observation in week 12, six out of seven patients were responders; among them, four were classified as remitters (MADRS <10). Unexpectedly,

the positive effects of sMFB were rapid. The mean MADRS was reduced by >50% at day 7 after onset of stimulation, and six of the seven patients had significant effects over only two days of stimulation. Previously, comparable acute and rapid effects in depression have been previously observed only in studies with the use of ketamine [27] or sleep deprivation [28]. Nevertheless, clinical studies report the clinical effect of ketamine is limited to two weeks [29], and the antidepressant effects of sleep deprivation alone are generally reversed after the next recovery sleep [30]. In contrast, the effects of sMFB DBS reported by Schlaepfer et al. [26] appear to be enduring. It is important to note that sMFB stimulation was linked only with appetitive motivation but was not associated with a direct reinforcing, hedonic or “liking” effects.

This recent data raises questions about the degree to which the various stimulation sites can be conceptualized as part of or an entry point into a single dysregulated neurocircuit or circuits. A recent preclinical study showed that despite similar antidepressant effects following stimulation to homologous SCG, NAc and MFB regions, they induce distinct changes in regional brain activity and functional connectivity [31]. The MFB may act as an integrative extension of other associative circuits underlying the pathophysiology of MDD to frontal structures [32]. Direct MFB stimulation thus may provide a shorter route to the prefrontal cortex and a speed access toward therapeutic reaction. The rapid onset of positive MFB DBS effects, if replicated, could not only be of great benefit for patients suffering from TRD but may also prove to be a factor in the search for the underlying mechanisms of fast-working antidepressant strategies [32].

POSSIBLE THERAPEUTIC MECHANISMS OF DBS FOR DEPRESSION

The therapeutic mechanisms of DBS in TRD are not well understood. Although research on the efficacy of DBS for TRD has been under way for approximately 10 years, it has typically been conducted in uncontrolled clinical trials, and the mechanisms mediating therapeutic effects are only more recently becoming apparent. Unlike DBS for movement disorders, therapeutic responses to

DBS for TRD occur slowly. Although patients may describe an immediate “insertional” effect, it is often followed by a sharp decline in symptom relief before the progressive and enduring improvement occurs [33]. Further complicating matters, the effects of DBS vary relative to the location of stimulation and stimulation parameters (voltage, pulse width, and frequency), as well as the overall activity state of the regions to be modulated [34–36].

With the exception of several imaging studies conducted during clinical trials, the majority of investigations of the mechanism of action of in high-frequency stimulation for depression have been conducted in small animal models of depression. The main mechanism is thought to facilitate a “resetting” of faulty circuitry in the CTSC pathway [33, 37, 38], which requires restoration of synaptic plasticity and facilitation of neurogenesis, known to be important mechanisms of antidepressant action. In addition to neurotransmitters, cytokines and growth actors have been implicated in the DBS-mediated antidepressant effects [39–41], occurring via gradual synaptic adaptations (plasticity) [42].

Cytokines

Inflammation and glial-mediated responses have been shown to play a key role in the therapeutic mechanism of DBS in a number of disease states, including Parkinson’s disease; however, little is known about their role TRD. Perez-Caballero et al. [41] shed light on this issue in a rodent model of depression in which electrode implantation in the infralimbic cortex (homologous to human SGC) was sufficient to induce an antidepressant effect as measured in the forced swim test. This effect was maintained for up to two weeks post implantation, after which active DBS was necessary to sustain a therapeutic response. These researchers were able to effectively block this therapeutic effect with anti-inflammatory pre-treatment and further demonstrated that an increase in astrocytes and inflammatory mediators up to two weeks after implantation correlated with antidepressant effects. Moreover, this inflammatory-mediated response was shown to enhance synaptic efficacy at serotonin synapses through upregulation of serotonin receptors and facilitation of serotonin signaling.

A rapid antidepressant response generated by DBS has been described as occurring prior to stimulation [11, 18] and has been attributed to the generation of a microlesion. However, a study by Perez-Caballero et al. [41] was the first to measure an insertional effect, the impact of anti-inflammatories, and long-term therapeutic responses to DBS. They reported differences in patient responses to bilateral DBS of SGC, which segregated according to anti-inflammatory treatment. Although early responses to DBS were similar for those patients receiving nonsteroidal anti-inflammatory drugs (NSAID) and those who were not, the antidepressant response began deteriorating after ~two weeks and was lost by one month post-DBS surgery for NSAID-treated patients.

Growth Factors and Synaptic Plasticity

It has been well established that growth factors such as brain derived neurotrophic factor (BDNF) are reduced in patients with depression, a finding documented as well in rodent models of depression [32, 43–45]. A subsequent increase in BDNF levels, in addition to changes in neuroplasticity, has been observed following successful antidepressant treatment and is thought to be a critical mechanism through which antidepressants exert their therapeutic effects [45, 46]. Similar results have been found in rodent models of depression following therapeutic DBS [39, 40, 47]. Not only are levels of BDNF increased, but morphological changes have been observed in the dendrites of prefrontal cortex (PFC) pyramidal neurons [42]. Interestingly, Hamani et al. [40] found a possible interaction between BDNF and serotonin, demonstrating that depletion of serotonin prevented the BDNF reduction that is normally seen in rats undergoing chronic mild unpredictable stress to induce depression-like behavior. This concept has been attributed to impaired stress adaption by the suppression of hippocampal glucocorticoid and BDNF responses [48]. However, Hamani et al. [40] also demonstrated that an animal's preference for sucrose, a measure of antidepressant efficacy, did not improve following DBS in serotonin-depleted rats with normal hippocampal BDNF. This suggests that although decreases in BDNF are seen in depression, and subsequent increases occur following antidepressant treatment, it is the interaction of BDNF with

serotonin systems, possibly mediated in part by inflammatory responses, that is critical to therapeutic response.

SUMMARY AND FUTURE DIRECTIONS

Each of the various DBS sites studied in the treatment of depression have been found to have some positive effects, and each appears to be associated with surrounding anatomic regions implicated in psychomotor, cognitive, mood, emotional and neurovegetative symptoms of depression (see Fig. 11.2). The differences in methods used to evaluate DBS efficacy among the studies reported to date prevent a consensus on the efficacy of a given target at this time. Larger controlled, DBS-ON/OFF clinical trials are needed to identify optimal targets, patient selection criteria, and the long-term effects on of DBS for depression, including the augmentation of social functioning, and normalization of brain metabolism. Such studies should also include the effects of DBS on standard measures of attention, learning, and memory. The potential for adverse events such as infection, suicide, and hypomania, also should be carefully monitored in the postoperative period. The studies reported to date represent an initial exploration of the potential of DBS as a therapeutic option for treatment-resistant depression.

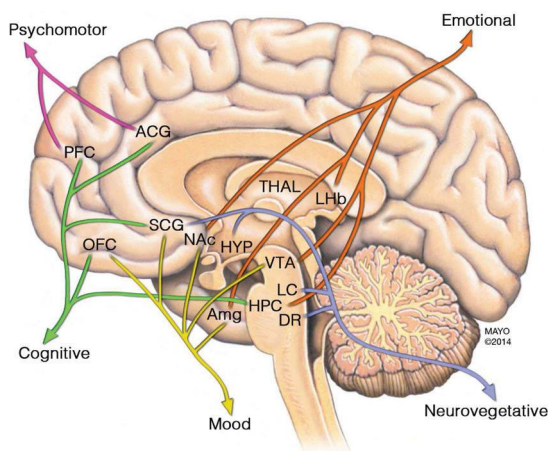


Figure 11.2 DBS sites and its surrounding regions' function in psychomotor, cognition, mood, emotions, and neurovegetation.

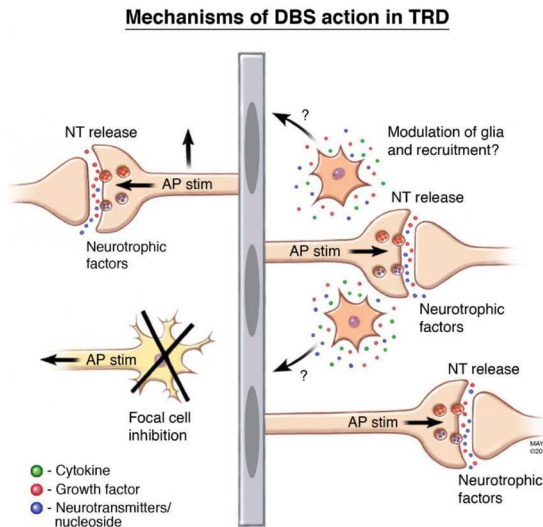


Figure 11.3 Proposed therapeutic mechanisms of DBS action in treatment-resistant depression. These mechanisms include, inhibition of local neuronal cells, activation of axons of passage and facilitation of neurotransmitter efflux, as is well established in the field of DBS for movement disorders. In addition, DBS activation of inflammatory responses and upregulation of neurotrophic factors is known to critically contribute to the progressive antidepressant actions of DBS for depression.

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Chapter 12

Deep Brain Stimulation for Chronic Pain

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INTRODUCTION: CHRONIC PAIN AND ITS CLASSIFICATION

Pain is an innate physiologic response intended to alert the body of either imminent or ongoing tissue injury. It has both qualitative (e.g., intensity and location) and affective components (e.g., withdrawal, crying, etc.). When pain occurs spontaneously (without a physical insult) or to non-painful stimuli, or when it continues beyond the expected time course for healing of an injury, it is considered pathologic. A pathologic perception of pain that persists and interferes with daily living or causes disability can generically be termed “chronic pain.” Using this broad definition, it is estimated that 1.5 billion people worldwide and 100 million Americans suffer from chronic pain [1, 2]. Comparatively, this is nearly a fourfold increase in the number of Americans with diabetes, a fivefold increase in the number with heart disease, and ninefold increase in the number with cancer.

Deep Brain Stimulation: Indications and Applications

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While a large percentage of the general population suffers from chronic pain, there is tremendous variability in etiology (e.g., cancer, trauma, stroke, etc.) and in the specific features of chronic pain disorders. Although clinicians generally agree on the various features of chronic pain disorders, the lack of a unified consensus [3] makes both the treatment and study of chronic pain disorders difficult. For ease of discussion, the pain literature classifies chronic pain disorders into two major categories, neuropathic pain and nociceptive pain. Neuropathic pain refers to any type of pain that arises directly from injury to either the central or peripheral nervous system. Thus, neuropathic pain is often further subcategorized into peripheral and central disorders. When there is an accompanying sensory loss due to damage of either the primary or secondary pain pathways, the term deafferentation is used. Nociceptive pain refers to pain that is relayed directly by nociceptors and the normal pain pathways [4]. It can also be further subcategorized into somatic and visceral pain.

PATHOPHYSIOLOGY

The pathophysiology of chronic pain disorders is not completely understood. In neuropathic pain disorders, there is often an inciting structural injury, such as stroke or trauma to the somatosensory system or pain processing areas [25]. However, damage to the nervous system does not always lead to the development of neuropathic pain, and pain can arise without injury. For example, pain disorders, such as fibromyalgia, appear to arise spontaneously or may be related to genetic or environmental factors [26]. Although etiologies vary, there are features common to chronic pain disorders that have led to the current prevailing theories. In neuropathic pain, for example, sensitization can lead to a lower threshold of activation in the neurons that transmit pain (peripheral or central) [27]. Sensitization results in hyperalgesia, allodynia (perception of pain with nonpainful stimuli), and spontaneous pain which is caused by the ectopic firing of neurons. Loss of inhibitory effects in descending pain pathways (disinhibition) and structural changes may also play a role in the development of chronic pain [27–30].

BRAIN STIMULATION FOR PAIN

The concept of using surgery to treat pain predates the modern era of functional neurosurgery. In the late 19th century, Rose and Horsley developed techniques to remove the gasserian ganglion to treat trigeminal neuralgia. Dorsal rhizotomy, selective destruction of dorsal roots of the spinal cord, also began at that time [5, 6]. However, the fortuitous discovery that direct electrical stimulation to the brain could relieve pain would not come until the 1950s. Attempting to modify behavior in psychiatric patients, R. G. Heath and colleagues applied an electrical stimulus to the right posterior septal region and found that patients not only experienced intense reward, but also noted temporary improvements in chronic pains [7, 8]. Since then, numerous other targets for deep brain stimulation (DBS) have been explored for the treatment of pain, including the posterior limb of the internal capsule, centromedian and parafascicular nuclei, the ventralis caudalis (Vc) of the thalamus, the periaqueductal/periventricular gray (PVG), pontine parabrachial region, the anterior cingulate cortex, and the nucleus accumbens (NAc) [9–17]. Presently, the most studied and commonly chosen DBS targets include the PVG and Vc, either alone or in combination [18].

Patient Selection and Evaluation

While the overall risks associated with DBS are low, it is an invasive procedure and carries with it the same potential for hemorrhage and infection that is associated with all surgery. There is no standard set of selection criteria for patients undergoing DBS for pain, but most physicians would agree that candidates should meet the following criteria [11, 18]. Foremost, the pain should be disabling or interfere with daily living. Second, patients should have failed to respond to nonsurgical measures, including adequate trials of accepted pharmacotherapies. “Failure to respond” is defined as pain persistence at maximum doses or the experience of intolerable adverse effects. Lastly, the presence of comorbid psychiatric disorders should be excluded, particularly those with neurotic or psychotic features. Patients

who have been appropriately treated for depression or anxiety (mild or moderate grade) can still be considered for surgery.

Candidates who meet these criteria should be carefully screened. At our institution, for example, patients undergo a comprehensive evaluation consisting of a detailed diagnostic interview and neurologic examination, psychiatric and pain consultation, neuropsychiatric testing, and appropriate imaging studies (MRI/CT) to rule out other etiologies [19]. Additionally, every DBS candidate undergoes formal review by the Mayo Clinic DBS committee, an interdisciplinary panel. If the patient meets criteria, DBS surgery is offered, recognizing that the efficacy varies considerably among different chronic pain syndromes. To gauge response to DBS, it is also imperative that validated baseline matrices be obtained prior to surgery. Examples include the Pain Disability Index, Visual Analog Scale scores, SF-36 scores, and the McGill Pain Questionnaire [19–23].

Various pain syndromes for which DBS has been tried and their relative response rates are shown in Table 12.1.

Table 12.1 Select pain syndromes that have shown response to deep brain stimulation

Select pain syndromes	Follow-up	Success rate	Study
Failed back syndrome (<i>N</i> = 13)	0.5–8 years	82% (≥50% relief)	Rasche et al. [18]
Phantom limb pain (<i>N</i> = 9)	31.9 months	89%	Boccard et al. [24]
Anesthesia dolorosa (<i>N</i> = 28)	1–180 months	29%	Bittar et al. [11]
Central Post stroke pain (<i>N</i> = 31)	23.1 months	69.6%	Boccard et al. [24]
Spinal Cord injury (<i>N</i> = 12)	0.5–5 years	20% (≥50% relief)	Rasche et al. [18]
Cancer pain (<i>N</i> = 23)	1–180 months	65%	Bittar et al. [11]
Brachial Plexus Avulsion (<i>N</i> = 7)	31 months	50%	Boccard et al. [24]

Target Selection

In general, the PVG is thought to be the most effective target for nociceptive types of pain, while the Vc is thought to be the most effective for deafferentation pain. Newer targets include the nucleus accumbens (NAc) or ventral striatum/ventral capsule and the anterior cingulate gyrus, which are thought to modulate the affective components of pain [15, 16, 31]. Further study is necessary to establish the efficacy of NAc and anterior cingulate stimulation and to determine which chronic pain disorders are responsive to these newer targets.

Surgical Procedure

At Mayo Clinic, DBS procedures for pain are performed under local anesthesia. After, numbing the scalp a Leksell head frame (Elekta, Norcross, GA) is placed, and the fiducial localizer box is secured. Preoperative MRI is obtained. Compass software (Compass International Innovations Inc., Rochester, MN) and a Schaltenbrand–Wahren atlas are also used for targeting. Typically, we use the combined PVG and Vc as the target for stimulation in chronic pain syndromes (Figs. 12.1A,B). In select cases, we have also targeted the NAc (Fig. 12.1C). The coordinates for each of these respective targets can be found in Table 12.2. After verifying our coordinates, a single skin incision that incorporates the planned target entry points is anesthetized. The skin is incised and 2 mm burr holes are made in the trajectory of each target. Microelectrode recordings are usually performed to guide electrode placement, followed by macroelectrode placement (Model 3387 leads; Medtronic, Inc, Minneapolis, MN).

Macrostimulation is performed to assess for adverse effects. With PVG stimulation, elevations in heart rate and blood pressure may be seen [32]. Dizziness and warm feeling have also been described with stimulation frequency of 50 Hz and a pulse width of 210 msec, and feelings of anxiety or panic may be seen if the amplitude is too high [18]. Euphoria, smiling, and laughter have been described with NAc stimulation [33, 34]. More details are in Table 12.2. Following macrostimulation, the leads are attached to extenders and externalized for test stimulation.

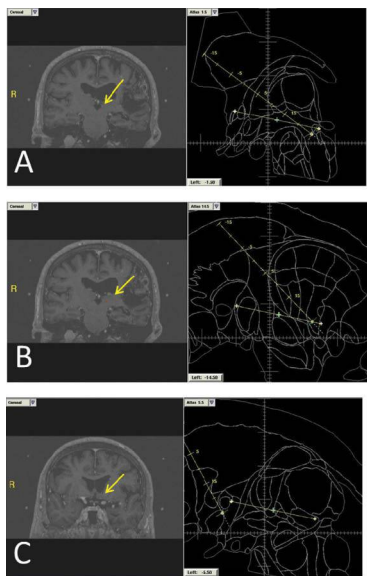


Figure 12.1 Preoperative MRI showing DBS targeting for central post-stroke pain. The periventricular gray (A), Ventralis caudalis of thalamus (B), and nucleus accumbens (C) are depicted in a coronal view with respective sagittal slices from the Compass targeting software.

Table 12.2 Deep brain stimulation targeting for pain

Targets	Coordinates	Adverse effects
Periventricular Gray (PVG)	• 2.5 mm lateral to the third ventricular wall • 2.5 mm anterior to PC • 2.0 mm inferior to ICL	• elevations in heart rate and blood pressure (normal) • gaze deviation or paralysis (too inferior to ICL) • Paresthesias (too posterior)
Vc	• 12 mm lateral to midline • 3.5 mm anterior to PC • 0.0 mm from the ICL	• pain with electrode placement of stimulation (normal) • paresthesias
NAc	• 7.0 mm lateral to midline • 1.0 mm anterior to AC • 4 mm inferior to ICL	• smell • dizziness, nausea • increased sexual drive • euphoria/laughter (normal, but subsides after several months)

Abbreviations: AC, anterior commissure; ICL, intercommissural; PVG, periventricular gray; PC, posterior commissure; Vc, ventralis caudalis of the thalamus.

Test Stimulation

Following, implantation the patient is observed in the intensive care unit. Test stimulation of each lead is performed in a double blinded fashion (neither the surgeon nor patient know which or if any leads are active) over a period of several days to a week. A careful pain log is kept by the nursing staff using visual analog scale scores. Typically, each target is stimulated at a given parameter setting for 3 hours. The stimulation parameters are adjusted as needed to achieve therapeutic effect. Adverse effects are also noted. The results of test stimulation determine which (if any) leads will be internalized and connected to the pulse generator for chronic stimulation. The patient then goes full implantation of their DBS system, and the device is turned on prior to discharge. Multiple return visits are often necessary for programming the stimulating parameters and device optimization.

POSSIBLE MECHANISMS OF PAIN RELIEF WITH DBS

The mechanisms by which DBS exerts its therapeutic effects have yet to be fully elucidated. The selection of the PVG as a target initially arose out of rodent experiments conducted by Reynolds et al. [35]. In these experiments, it was demonstrated that a laparotomy could be performed without evoking pain with continuous stimulation of the periaqueductal gray (PAG). It was later discovered that stimulation of PAG in both humans and animal models increased cerebrospinal fluid (CSF) opioid metabolites and that reversal of stimulation-induced analgesia could be obtained by administering naloxone [36, 37]. However, because PAG stimulation also causes oscillopsia and gaze palsies, and only ventral stimulation provides relief, it was decided that it was best to target the PVG, which is also part of endogenous opioid system, but slightly more rostral.

Based on these experiments and known descending projections to the raphespinal and reticulospinal nuclei, it was initially hypothesized that pain relief occurred solely by activation of descending endogenous opioid pathways [38–40]. However, it is now recognized that activation of ascending tracts to the

intralaminar nuclei, reticular nucleus, mediodorsal nucleus of the thalamus, and prefrontal cortex may also play a role [38–40]. Functional imaging studies show medial thalamic, cingulate, and prefrontal activation during DBS in correlation with analgesic responses [39, 41, 42]. Thus, PVG stimulation likely exerts its analgesic effect by modulating both ascending and descending pain pathways.

Targeting somatosensory pathways was initially proposed by Mazars et al. [43]. In addition to producing paresthesias, it was noted that an analgesic response also occurred with both stimulation of the posterior limb of the internal capsular and with Vc stimulation. Most surgeons now target Vc because it produces a more reliable response and is easier to target [44]. The analgesic effect of Vc stimulation has been shown to be partially mediated by descending projections. This concept is supported by the observation of stimulation-induced serotonin release in the spinal cord and by a loss of DBS-evoked analgesia with selective lesioning of the upper cervical cord [45, 46]. However, both PET and functional MRI also show cortical activation with Vc stimulation, particularly in the anterior cingulate gyrus and primary somatosensory cortex [41, 47].

The NAc is gaining favor as a DBS target for obsessive compulsive disorder and depression [48, 49] but is also known to play a role in mediating pain processing. In particular, the NAc has been involved in the placebo response [50]. Short-term analgesia has been reported with sole NAc stimulation, although at our institution it is chosen as an adjunctive target due to the limited available evidence of its efficacy [16]. Machado et al are currently investigating its efficacy for thalamic pain syndrome [51]. NAc stimulation has been shown to produce blood-oxygen-level-dependent (BOLD) signal change in the cingulate, prefrontal, and insular cortices, areas that mediate the affective response to pain [52]. Thus, it is thought that NAc stimulation may modulate the emotional response to pain.

Interestingly, there appears to be some overlap in activation of the cingulate region with all targets. The anterior cingulate cortex mediates the affective component of pain and has been previously intentionally lesioned to treat cancer pain [53, 54]. Direct stimulation of the anterior cingulate is also now being proposed as potential treatment for chronic pain [55, 56].

While the precise mechanisms of pain relief with DBS are not yet fully understood, the evidence suggests that analgesia can be obtained by modulated either descending and/or ascending pain pathways or by selectively targeting areas that mediate the affective response to pain (e.g., anterior cingulate, NAc). Further research exploring the mechanisms of DBS-evoked analgesia is needed. Advances in neuromonitoring techniques (e.g., cyclic voltammetry for neurotransmitters) and functional neuroimaging will allow for a more detailed understanding of the effects of DBS on neural network activity [57].

LONG-TERM EFFICACY OF DBS FOR PAIN

A variety of chronic pain syndromes have shown favorable responses to deep brain stimulation. However, the exact role of DBS relative to other treatments (e.g., motor cortex stimulation) is not known, nor has the use of DBS been fully validated in open label prospective trials. The initial studies to obtain FDA approval were performed in the 1990s and failed to meet their primary objectives for implantation rates (>50%) and predetermined response rates [58]. Although several factors likely contributed to their failure to meet objectives (e.g., study design, attrition, non-uniform selection criteria, and heterogeneity), further effort has not been made to obtain FDA approval. Therefore, DBS for chronic pain remains an off-label indication. As a result, a large portion of subsequent studies have been lacking in quality and numbers. Most such studies consist of retrospective, nonrandomized, unblinded, and heterogeneous single institution cohorts. Additionally, not all series relay how many patients are excluded from full implantation after test stimulation, which likely overestimates the efficacy of DBS for pain. For example, only 77% of the cohort examined by Kumar et al. (1997) was fully implanted for short- and long-term outcome assessments [59]. Few studies use validated outcome measures and have adequate follow-up. All of these factors limit the conclusions that can be made regarding the efficacy for DBS for pain.

The long-term success rates for DBS for chronic pain vary from 38–90% (Table 12.3) [10, 12–14, 18, 24, 59–62]. A more recent study by Boccard et al. (2013) in the U.K. found long-term (mean follow-up = 20 months) success rates of

66–89% using validated outcome measures. Efficacy depended on the type of pain syndrome, with post stroke pain having a 70% success rate and phantom limb pain having an even higher success rate of 89% [24]. It is felt that combined stimulation of PVG/PAG with Vc is more effective than stimulation of either target alone. In a meta-analysis of over 200 patients Bittar et al. (2011) found that combined stimulation had a success rate of 87% compared to 58% with sole Vc stimulation [11]. Because of the variable response rates, our institution has adapted the approach to implant all three targets and chronically implant electrodes on the basis of test stimulation.

Table 12.3 Long-term success rates of DBS for pain

Author and year	No. of patients	No. of patients implanted for chronic stimulation	Follow-up (months)	Long-term success rate (no. of successful cases/# undergoing chronic stimulation)	DBS lead location
Richardson et al., 1997 [12, 13]	8	7	1–42	86%	PVG
Tumbull et al., 1980 [14]	18	14	1–47	86%	ST
Young et al., 1985 [60]	48	43	2–60	81%	PVG/PAG/IC/ST
Hosobuchi et al., 1986 [10]	122	105	24–168	90%	PAG/ST
Levy et al., 1987 [61]	141	83	24–168	51%	PAG/IC/ST
Kumar et al., 1997 [59]	68	53	6–180	79%	PVG/PAG/IC/ST
Hamani et al., 2006 [62]	21	13	3–108	38%	PVG/PAG/Vc
Rasche et al., 2006 [18]	56	34	12–96	62%*	PVG/VPL/VPM
Boccard et al., 2013 [24]	85	59	6–42	66%	PVG/VPL

Source: Adapted from Bittar et al. [11].

*Only patients with at least 50% VAS improvement were included.

SUMMARY AND FUTURE DIRECTIONS

Deep brain stimulation should be considered as a treatment option for patients with refractory chronic pain. However, more prospective and, preferably, blinded studies using validated outcome measures with sufficient long-term follow-up are needed to confirm its efficacy. Additionally, future work should address which targets should be chosen for select pain disorders, especially newer and less established targets. Lastly, research aimed at determining the mechanisms by which DBS alleviates pain should continue.

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Chapter 13

Deep Brain Stimulation for Medically Refractory Epilepsy

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INTRODUCTION

Epilepsy is the most common acute neurologic problem in the United States [1] and one of the most prevalent neurological illnesses in the world, affecting an estimated 1% to 3% of the global population [2]. A 2000 study estimated that the economic burden of epilepsy in the United States alone exceeds \$12 billion per year [3, 4]. Individuals with epilepsy report significantly lower scores on health-related quality of life measures than the general public, and their scores decrease as a seizure frequency increases [5]. Repeated seizures may lead to impaired cognitive performance, which can affect social interaction and employment. Epilepsy in general is associated with a two- to three-fold increase in mortality, and patients with uncontrolled seizures have up to a 40 times greater risk of mortality than those whose seizures are controlled [6]. In approximately 40% of patients, the cause of death

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is thought to be directly related to epilepsy [7] and may include the underlying causative neurologic disorder, accidents during a seizure, status epilepticus (i.e., continuous seizures of longer than 5 min duration), suicide, treatment-related death, and sudden unexpected death in epilepsy (SUDEP).

Despite advances in modern antiepileptic drug therapy, approximately 30% of adults with epilepsy remain refractory to medical treatment [8], and there is considerable interest in developing alternative therapies, surgical and otherwise. Dietary modifications [9], immunotherapy [10], and extracranial electrical stimulation of either the vagus or trigeminal nerve have all emerged as interventions with therapeutic potential that is beginning to be realized. Since the preliminary cerebellar stimulation studies by Irving Cooper in the late 1970s, intracranial electrical stimulation, which includes both deep brain stimulation (DBS) and cortical neurostimulation, has also made important advances in the treatment of medically refractive epilepsy [11, 12].

While there have been numerous case studies and small, uncontrolled studies reporting on the efficacy of a plethora of stimulation targets for epilepsy, this chapter focuses on the targets and techniques that are supported by controlled, blinded clinical trials. We will also briefly discuss the investigational rationale for target choice, current theories of the therapeutic mechanism, and the most pertinent areas of future research in neurostimulation for epilepsy.

BACKGROUND AND PATHOPHYSIOLOGY

The term “epilepsy” refers to a predisposition to experience recurrent unprovoked seizures [13], which are episodes of abnormal, excessive or synchronous neural activity. Epilepsy is classified by its clinical features, which include coexisting conditions, history of onset, the frequency, severity and duration of seizures, and by the cause and locus of seizure onset. Epilepsy and the seizures associated with them can be divided into three broad categories: (1) primary generalized, (2) partial (with a focal onset), and (3) undetermined. Seizures can also be categorized by the type of physical response they elicit, such as atonic (loss of muscle tone), tonic (increased muscle tone and stiffening), and clonic (repeated jerking).

Primary generalized seizures arise simultaneously in both cerebral hemispheres without a known or testable locus of origin and typically result in a major motor seizure, but can also manifest as a brief moment of unconsciousness called “petit mal” or “absence” seizures. Primary generalized seizure disorders typically have a strong genetic component, and patients often present with otherwise normal neurologic function [13].

Partial seizures arise from a distinct brain locus and can be either simple or complex. Simple partial seizures typically remain localized to the site of onset, usually the temporal or frontal lobe, and do not cause loss of consciousness. Symptoms of partial seizures vary according to the locus of origin in the brain and the functions it controls.

Complex partial seizures may arise from any part of the brain, but like simple partial seizures, most often begin in the frontal and temporal lobes. In complex partial seizures, abnormal electrical activity spreads to other brain areas and can interfere with consciousness. Partial epilepsy syndromes may occur following an insult to the central nervous system, such as trauma, hypoxia, stroke, tumor, or venous malformation, but the cause is not always identifiable [13]. Because complex partial seizures are often refractory to medical therapy, patients with this type of seizure activity may be candidates for surgical intervention.

Diagnosis of a seizure disorder is based on patient history, the presence of accompanying neurological or developmental abnormalities, and on the clinical features of the seizures as visualized on electroencephalographic (EEG) recordings [13]. Brain imaging helps to localize seizures and to determine whether there are space-occupying lesions, such as a tumor, or other abnormalities, such as a cavernous angioma or areas of atrophy that could be causing the seizures. Other important diagnostic procedures used include neuropsychological testing, a psychosocial assessment, video-EEG recordings, and brain mapping for potential surgical patients.

While over 80% of patients with primary generalized epilepsy achieve seizure control through anti-epileptic drugs (AEDs), only 50% of patients with partial epilepsy are successfully treated with them [14]. AEDs are numerous, and new additions are constantly being developed. Fourteen novel AEDs have been introduced in the United States since 1993 [15]. However, once two or three

established drugs have failed, few patients with drug-resistant partial epilepsy respond to the newer pharmacotherapies [16].

Surgical resection, which removes or isolates brain tissue involved in seizure generation, can be considered an effective option for carefully screened patients [17]. The most common form of epilepsy surgery, the anterior temporal lobectomy, is highly invasive and carries the risk of post-operative verbal memory decline [18]. The goal of surgical resection is to remove the epileptic tissue without causing neurologic deficits. There are a number of presurgical and perioperative techniques used to determine if surgical resection will spare or compromise eloquent tissue (i.e., cortical areas critical to sensory, motor, cognitive, and linguistic function), and thus not all patients with localized seizures are good candidates for such a procedure.

For these patients, another option is neurostimulation, which is less invasive and is reversible. Both DBS and cortical stimulation have the potential to modulate neural networks distal from the stimulation site, which make them a promising approach for patients with intractable epilepsy.

Studies using high-frequency stimulation (HFS), like that used in DBS, have been found to abolish seizure-like synchronous neuronal discharge. It is thought that HFS-mediated glutamate and adenosine release may be important in the ability of DBS to abolish synchronized neural network oscillations. Lee et al. [19] found that HFS resulted in a marked depolarization of thalamocortical neurons and abolished both spindle and 3 Hz absence seizure-like oscillations. Using an enzyme-linked glutamate sensor system and fast scan cyclic voltammetry (FSCV) [20–25], extracellular glutamate and adenosine levels were seen to rise during HFS in the ferret thalamic slice and to abolish spontaneous spindle oscillations [26]. It has been suggested that HFS-induced gliotransmitter release in the thalamus or subthalamic nucleus [27] may “jam” abnormal oscillations that lead to tremor and absence epilepsy.

DBS relies on “open loop” stimulation, in which stimulation is applied continuously or according to a pre-set pattern. Cortical stimulation or what is called “responsive neurostimulation” (RNS) relies on feedback-responsive or “closed-loop” stimulation, in which stimulation occurs only at the onset of a seizure. Each method has unique advantages in the treatment of epilepsy. Recently, two

large multicenter randomized, double-blinded clinical trials of intracranial stimulation for epilepsy were conducted. The first was a study of continuous, open-loop DBS of the anterior thalamus; the second, a study of RNS of cortical seizure foci, using an electrophysiological sensing system that applies stimulation only at the onset of a seizure [28, 29]. Together, these trials comprise the only class 1 evidence-based approaches for intracranial neurostimulation in epilepsy. Anterior thalamic DBS was recently approved in Europe, and an RNS device was recently granted FDA approval. The following sections review the rationale and results to date for each type of neurostimulation.

DEEP BRAIN STIMULATION OF THE ANTERIOR THALAMIC NUCLEUS

Connectivity and Rationale

The anterior thalamic nucleus (ATN) is the most extensively studied DBS target for the treatment of epilepsy. As a part of the Papez circuitry pathway, the ATN connects to the cingulate gyrus and receives input from the mammillary body via the fornix and then connects to the entorhinal cortex and back to the hippocampus [30]. By virtue of its connectivity with mesial temporal and orbitofrontal structures via the cingulum bundle [31], the ATN represents an attractive DBS target for epilepsy from a network modulation perspective (Fig. 13.1).

The Papez circuitry is known to play a central role in the generation and maintenance of epileptic activity. The role of the ATN and mammillothalamic tract in these processes was first addressed in a guinea pig model in which seizures are induced by systemic administration pentylenetetrazol (PTZ), a GABA antagonist. Imaging studies of the model revealed metabolic hyperactivity of the mammillothalamic tract and ATN during seizures [34]. In addition, it was found that both interruption of the mammillothalamic connection and pharmacological inhibition of the ATN with GABA agonists were able to protect against PTZ-induced seizure discharges, as well as abort ongoing seizures [35, 36].

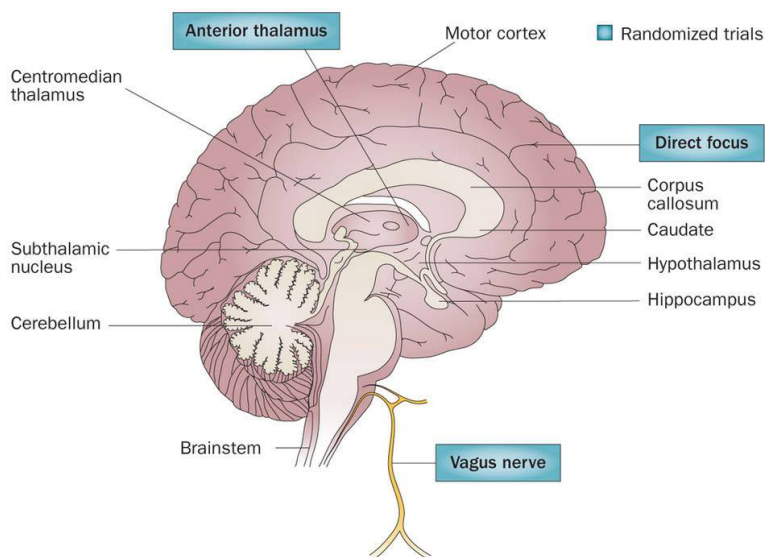


Figure 13.1 DBS targets for the treatment of medically refractory epilepsy. Reprinted with permission from [32, 33].

Numerous studies of animal models of epilepsy, using a variety of seizure-producing agents and techniques, point to the therapeutic potential of electrical stimulation of the ATN. For example, low-frequency stimulation of bilateral ATN was shown to inhibit seizures [37], and both unilateral and bilateral ATN DBS has been shown to decrease seizure frequency [38]. There are also some laterality effects that suggest that left and right ATN may play different therapeutic roles [39]. Bilateral, but not unilateral ATN DBS significantly delayed the time to onset of status epilepticus after the administration of pilocarpine [40], and left-sided stimulation has been found to increase threshold for the development of status epilepticus. However, another study in which chronic seizures were induced by systemic KA administration saw an increase in seizure frequency with ATN DBS [41]. It has also been shown in the PTZ rat model that electrical stimulation of the mammillary bodies could increase seizure threshold [42]. High-frequency (100 Hz) stimulation of the ATN showed similar results, and it was also noted that low-frequency stimulation (8 Hz) of this structure in the rat was actually proconvulsant [43]. In human studies, the ATN is a more attractive surgical target than the

mammillary bodies due to the high hemorrhage risk inherent in targeting the latter structure, which is located close to the Circle of Willis.

Structural imaging studies in humans have further implicated areas of the Papez circuitry, and the ATN in particular, in seizure pathology. MRI-based methods in patients with mesial temporal sclerosis have identified structural abnormalities in a variety of Papez circuitry elements, including the hippocampus, parahippocampal gyrus, fornix, mammillary bodies, thalamus, cingulate gyrus [44], and bilateral anterior thalamus volume loss has been found to correlate with volume loss in the CA1 region of the hippocampus and thinning of the mesial temporal cortex [45]. When patients with idiopathic generalized epilepsy were monitored by simultaneous EEG and functional magnetic resonance imaging (fMRI) during spike-and-wave discharges, both ATN and centromedian-parafascicular (CM-Pf) thalamic nuclei were activated after the initiation of spike-and-wave discharges, suggesting a possible role for the ATN in propagation of generalized seizures [46]. Taken together, studies of both animal models of epilepsy and of human patients with epilepsy provide a strong therapeutic rationale for targeting the ATN in DBS.

Clinical Evidence: The SANTE Trial

While animal studies have provided a solid rationale for the use of ATN DBS in humans, they are limited in their ability to precisely emulate human epilepsy. The earliest human ATN DBS studies were conducted by Cooper et al. in the 1980s. In a pilot study, six patients with partial epilepsy were treated with bilateral continuous ATN DBS and four had statistically significant reductions in seizure frequency, while one became seizure-free [47, 48]. Subsequently, six unblinded studies yielded a mean 47% reduction in seizure frequency among 28 participants [49–54].

These promising preliminary results motivated the establishment of the first large multicenter randomized double-blind trial for ATN DBS, which was called the “Stimulation of the Anterior Nucleus of the Thalamus (SANTE)” project, the results of which were published in 2010 [28]. This trial included 110 adults with focal seizures, including secondarily generalized seizures (i.e., focal onset seizures that generalize to the whole brain). All

patients had at least 6 seizures per month and up to 10 per day, and all had failed at least three antiepileptic drugs.

A 3-month blinded phase in which half the participants received stimulation and half received sham stimulation was followed by an unblinded phase in which all participants received therapeutic stimulation. Stimulation parameters consisted of 1 min of 90 μ s pulses of 5 V at 145 Hz interleaved with 5 min without stimulation. The results showed that during the last month of the blinded phase, the stimulated group had 29% greater seizure reduction than the sham group. After two years of open-label stimulation, there was a 56% median reduction in seizure frequency, and 54% of patients experienced seizure reduction of 50% or more. Five-year follow-up results indicate that the therapeutic effect is long-term: median seizure frequency improved by an average of 69% [55]. The finding of a 14.5% median decline in seizures in the sham group during the blinded phase suggests that a microlesion or placebo effect may be involved. However, the progressive improvement in average treatment response over time indicates that stimulation may be exerting an important therapeutic effect.

Only 7.3% of patients in the trial were seizure-free for more than one year, suggesting that perhaps optimal stimulation parameters for this therapy have yet to be identified. Participants in the stimulation group were more likely to report memory problems or depression, with two participants experiencing acute stimulation-induced seizures. Patients with temporal seizure foci reported greater benefit than patients with extratemporal foci during the blinded phase, in line with neuroimaging and electrophysiology studies, which consistently show that ATN DBS modulates brain activity within mesial temporal structures.

At present, ATN DBS is approved for the treatment of refractory partial epilepsy in several countries including those in the European Union. In Europe, ATN DBS is offered to adult patients ranging from 18 to 65 years of age who have medically refractory, focal-onset epilepsy that has resulted in significant impairment in quality of life for at least 12–18 months. Patients with between 6 seizures per month and 10 seizures per day are considered, and both surgical resection and vagus nerve stimulation must be either considered or trialed unsuccessfully before going forward

with DBS. The treatment is not currently approved in the United States. Although the first application submitted in 2010 for FDA approval was unsuccessful, a resubmission to the FDA is pending, given the favorable long-term follow-up results reportedly obtained from SANTE trial participants [55].

ATN DBS: Theories of Mechanism

While the SANTE trial provided Class 1 evidence in support of the efficacy of ATN DBS for the treatment of refractory partial epilepsy, its therapeutic mechanisms remain elusive, as do those for other DBS treatments. General theories about the therapeutic mechanisms of DBS are discussed elsewhere in this book. Here we will discuss investigations of mechanism specifically pertaining to DBS of the ATN.

A handful of studies using electrophysiological, magnetic, and functional imaging approaches in patients and in animals support the notion that ATN DBS affects neuronal activity in multiple cortical areas distal from the site of stimulation, including ipsilateral parahippocampal, entorhinal, and cingulate cortices. Cooper et al. investigated metabolic responses resulting from ATN DBS using (18F) 2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in two patients and found that ATN DBS increased regional glucose uptake in the limbic system [47, 48]. These findings suggest that network activity within the Papez circuitry is being affected by ATN DBS. In an electrophysiology study of a patient with an implanted ATN DBS system and mesial and lateral temporal depth recording electrodes, Zumsteg et al. found that high-frequency (>70 Hz), high voltage (>7 V) stimulation caused significant inhibition of ipsilateral mesial temporal structures, as measured by a decrease in cross power spectral density [56]. Using depth electrode recordings in two additional patients, they demonstrated that ATN DBS resulted in cortical activation within the mesial temporal and orbitofrontal cortices [57]. An EEG-based method further confirmed that DBS evoked activation of neurons within cingulate cortex, insula, and lateral neocortical structures [58]. While the ATN has established connectivity with some of these structures (e.g., mesial temporal, cingulate), others (e.g., insula) do not have established direct connections with ATN.

Therefore, it is possible that stimulation is indirectly affecting brain regions outside of the Papez circuitry through polysynaptic modulation.

To investigate the cortical effects of ATN DBS, Molnar et al. compared transcranial magnetic stimulation-induced short-term intracortical inhibition (SICI) in patients with DBS on vs. DBS off, and found that ATN DBS increases SICI in motor cortex, suggesting that electrical stimulation may result in up-regulation of GABAergic interneurons in the cortex [59]. This mechanism would likely work through a polysynaptic pathway, since the cingulate cortex is known to project to motor cortex and to play a role in the selection of voluntary movement [60]. Bilateral ATN lesioning or stimulation has been found to suppress clinical seizures in a kainic acid seizure model and mitigate seizure-induced glucose uptake in the sensorimotor cortex, striatum, thalamus, mammillary body, and midbrain tegmentum [38]. Thus, preliminary evidence suggests that ATN DBS may modulate not only mesial temporal structures, but also other cortical regions less classically associated with seizure generation. However, whether DBS therapy inhibits neural activity through activation of GABAergic neural activity or by stimulating release of other inhibitory neurotransmitters or potentially by functional inactivation of glutamatergic thalamic projections remains to be determined. Liu et al. found that ATN stimulation was capable of normalizing increased glutamate and increased GABA concentrations in the ipsilateral hippocampus [61]. These results indicate that ATN DBS may act by normalizing pathological neurotransmitter levels distal to the site of stimulation. However, further work will be needed to elucidate the neurochemical correlates of this therapy.

CENTROMEDIAN NUCLEUS AND OTHER DBS TARGETS

The centromedian (CM) nucleus of the thalamus is an intralaminar thalamic nuclear complex, a set of structures known to be part of the ascending reticular activating system (ARAS) which is thought to mediate the conscious state [62] (Fig. 13.1). The CM nucleus has a high level of direct connectivity with the basal ganglia and anterior insula [63]. Electrical stimulation of the CM was found to

be capable of inducing desynchronization on cortical EEG scans in cats [62]. Since primary generalized epilepsy syndromes are characterized by cortex-wide synchronization of neural activity, the CM was chosen as a promising candidate DBS target for the treatment of primary generalized epilepsy.

The first report of CM stimulation for the treatment of refractory generalized and multifocal epilepsy comprised a series of five patients. Cyclic (1 min on, 4 min off) stimulation with alternating laterality was delivered at high frequency for 2 h per day and resulted in an average of a greater than 80% reduction in seizures [64]. Fisher et al. conducted a double-blind, crossover study in seven patients to further test the efficacy of CM DBS. Cyclic stimulation (1 min at 5 V 65 Hz, 90 μ s, 4 min off) versus sham stimulation was administered for 3 months, followed by a 3 month washout period in which patients crossed over to the other treatment group [65]. Average seizure frequency decreased from baseline by 30% during the treatment phase versus 8% during the sham phase. This difference was not statistically significant. However, one patient in the treatment group declined to cross over to the sham group after receiving a significant benefit from treatment, which may have affected the results, given the small number of subjects in this trial.

Another study repeated this stimulation paradigm in five patients with mixed medically refractory seizure types, and found an average of 90% reduction in seizure frequency. While patients with generalized tonic-clonic seizures experienced a significant reduction, those with complex partial seizures did not [66]. In a crossover study similar to that designed by Fisher et al., five patients had frontal and six had generalized epilepsy [67]. Although all six patients with generalized epilepsy achieved >50% reduction in seizures during open-label stimulation, only two of the five frontal patients achieved a similar level of seizure reduction. These results provide preliminary evidence in support of CM DBS for generalized as opposed to partial syndromes. However, Class 1 evidence for this treatment has yet to be obtained, nor has it been obtained for the many other promising cortical and subcortical DBS targets recently investigated, which include the hippocampus, caudate, subthalamic nucleus, and cerebellum (Fig. 13.1) [32].

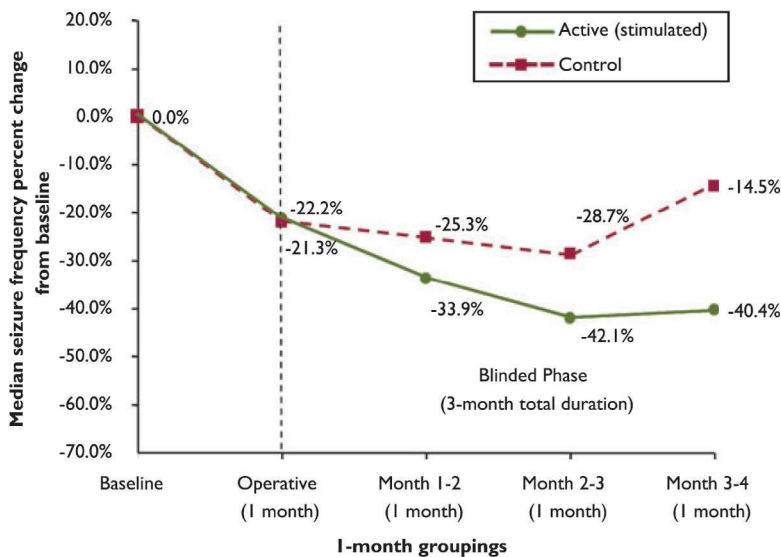


Figure 13.2 SANTE Trial: Results from blinded phase. From [28].

RESPONSIVE NEUROSTIMULATION

Rationale

Responsive neurostimulation (RNS) represents an alternative strategy for intracranial neurostimulation. While DBS targets network nodes, theoretically allowing the stimulation to act on epileptic networks, in RNS, the seizure focus itself is directly stimulated. As mentioned earlier, DBS uses an “open-loop” strategy in which stimulation is applied either continuously or in a predetermined cyclic pattern. In the “closed-loop” or feedback-driven stimulation of RNS, however, one or two sensing electrodes are programmed to recognize the changes in local field potentials that occur at the onset of a seizure and to respond with stimulation through either the same electrode or a second electrode. RNS system contains a skull-mounted neurostimulator connected to one or two leads capable of sensing and stimulating. These leads may be subdural strips, or depth electrodes. In theory, the RNS strategy may be superior to a continuous stimulation paradigm, which depletes pulse generators more quickly and may carry a greater risk of long-term adverse effects.

In 1954 Penfield and Jasper reported that intraoperative electrical stimulation of the exposed cortex could inhibit local electrocorticography signals, including both normal and epileptic discharges [68]. In a 1999 study, Lesser et al. showed in 17 patients undergoing preoperative evaluation with subdural electrodes that stimulation-induced after-discharges could be aborted by applying a train of brief stimulus pulses [69]. These observations opened the possibility of using direct stimulation of eloquent cortex for the treatment of epilepsy.

RNS for epilepsy was first tested in computational models and in open-loop stimulation of seizure foci in humans. Human studies were initially conducted in patients implanted with subdural and depth recording electrodes to monitor seizures prior to epilepsy surgery. In 2006, direct cortical stimulation was used to successfully treat a patient with a frontal epileptic focus [70], and six additional patients with foci in motor and supplementary motor cortices were also treated in this manner [71, 72]. While these trials illustrated the promise of direct stimulation of eloquent cortex to abort seizures, they used an open-loop design similar to DBS.

The potential of “smart” or closed-loop neurostimulation technology to abort seizures was first discovered in studies of animals and in computational models. A study of rat hippocampal slices demonstrated the feasibility of using a computer-controlled system to apply current in response to abnormal electrical activity [73]. Computational studies that model network burst firing caused by hypersynchronized neural activity supported the idea that electrical stimulation of epileptic networks could theoretically interfere with network burst-firing [74, 75]. An RNS device, the NeuroPace RNS system (NeuroPace, Inc., Mountain View CA), showed initial promise in a 2004 pilot study of four patients using an external processor-stimulator in which seizure frequency was reduced by 50–75% [76]. A subsequent implantable model was developed in which one or two depth or subdural electrodes are implanted in cortical seizure foci with a skull-mounted unit that processes electrophysiological data and contains a pulse generator [77]. An initial feasibility and safety study in 65 patients found the device to be safe [78], setting the stage for a randomized, controlled trial [29].

Clinical Evidence: Responsive Neurostimulation

The results of the first multicenter, double-blind, randomized, controlled study of RNS for partial epilepsy were published in 2011 [29]. Called the “NeuroPace” trial after the manufacturer of the stimulator, the study included 191 adults with medically refractory partial epilepsy across 31 institutions. The subjects averaged three or more seizures per month. Thirty-two percent of them had undergone prior epilepsy surgery, and 34% had prior VNS implantation. After a 1 month training period, implanted subjects were randomized to stimulation ON and OFF groups, and underwent a 3 month blinded evaluation phase followed by open-label evaluation, as in the SANTE trial. During the blinded phases, seizures were reduced by 37.9% in the treatment group compared to a reduction of 17.3% in the sham group. Open-label stimulation revealed a progressive decline in seizure frequency in the treatment group, and the sham group reported a significant reduction in seizure frequency in the month immediately following the transition to open-label stimulation (Fig. 13.3). Average seizure reduction rates were 44% at one year and 53% following two years of stimulation, indicating a progressive long-term response to RNS [79].

The trend toward progressive reduction in seizure frequency over time, and the finding that the treated group improved compared to the sham group during the 3 month blinded period bears striking similarity to the results of the SANTE trial for ATN DBS. Both trials also reported transient implantation effect in the sham groups, with a 14.5% and 17.1% reduction in seizures in the SANTE and NeuroPace trials, respectively. Whether this “implantation” effect is due to microlesioning, a placebo effect, or to some other aspect of surgery, such as anesthesia, is unclear [80, 81]. However, transient improvement in seizure frequency following lead implantation appears to be a consistent theme in neurostimulation for epilepsy. The effect does indeed appear to be transient, with a 25.2% reduction in seizure frequency after 1 month of sham stimulation reducing to a 9.4% reduction after 3 months in the NeuroPace trial. Rates of seizure freedom over 6 months were somewhat greater in the NeuroPace trial compared with the SANTE trial (20% vs. 12%, respectively).

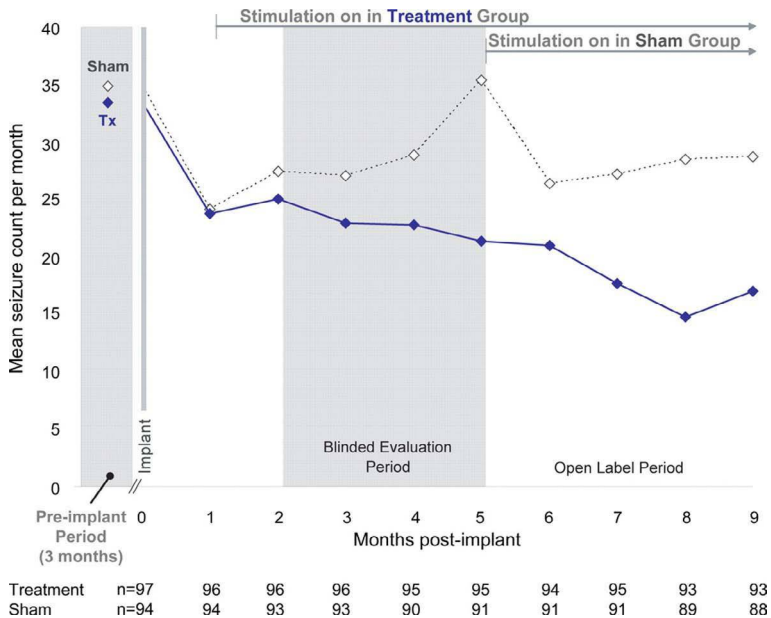


Figure 13.3 RNS trial results. From [29].

FUTURE DIRECTIONS

One of the challenges of DBS for the treatment of epilepsy is that, unlike DBS for movement disorders, such as Parkinson's disease or tremor, physicians do not have reliable methods for determining optimal stimulation parameters. Popular parameters to date for stimulation have been based trial and error using the parameters considered effective in the treatment of movement disorders (1–5 V, 60–200 μ s, 120–180 Hz). However, selection of optimal stimulation parameters in DBS for epilepsy remains a problem due to limited understanding of the underlying mechanism of the therapy. For example, uncertainty remains over whether low or high-frequency stimulation is more effective and whether cycling paradigms are superior to continuous stimulation. One study examined the effects of varying both stimulation frequency and amplitude on the success of ATN DBS in delaying the onset of status epilepticus in the pilocarpine-induced epilepsy rat models. Varying the stimulation current (between 200 μ A and 1000 μ A)

was found to have a greater effect than varying frequency (20 Hz vs. 130 Hz) [82]. In a study of a sheep model of epilepsy involving the administration of penicillin, a GABA antagonist, ATN DBS at frequencies at or above 80 Hz suppressed hippocampal epileptiform activity. In addition, seizure suppression persisted after termination of stimulation, such that seizure activity returned to at least half the pre-stimulation level after 5 min. This study provides support for the parameters used during the blinded phase of the SANTE trial (5 V 145 Hz, 90 μ s; 1 min on, 5 min off [83]. In an electrophysiology study of a single patient with ATN DBS for the treatment of limbic seizures, stimulation resulted in ipsilateral mesial temporal inhibition that occurred with a latency of approximately 60 s post-stimulus onset, but that would stop immediately upon termination of stimulation [56]. These results suggest that perhaps cycling paradigms, such as those employed in the SANTE trial, may not be as favorable as paradigms that use a longer ON period, or perhaps even continuous stimulation.

Another potential benefit of DBS parameter optimization is minimization of adverse effects. However, it is worth noting that DBS for refractory epilepsy appears to have a very favorable adverse effect profile compared to that of AEDs, which can generate an average of 6.5 medication-related adverse effects. Of these, impaired cognition and coordination have the greatest negative impact on quality of life [84].

The NeuroPace trial did not report any significant differences in adverse effects between treatment and sham groups. On the other hand, the SANTE trial reported increased rates of depression in the treatment group compared to sham group (14.8% vs. 1.8%) as well as memory impairment (13% vs. 1.8%). However, whether these adverse effects were truly stimulation-induced is questionable because patients with refractory epilepsy are at a high risk for depression and memory deterioration. In addition, almost all the patients who developed depression in SANTE trial had a baseline history of the condition. While further studies are needed to determine the risk of these adverse effects, the risk must be balanced against those inherent in uncontrolled epilepsy, which include neuropsychiatric impairments and sudden death.

Further study is also needed to determine the long-term effects of intermittent electrical stimulation. In the case of RNS

in particular, a higher current density than that applied during continuous stimulation can be tolerated. However, the long-term effects of applying current densities on the order of 50–60 mC/cm²/phase have yet to be elucidated. There exists considerable concern that such a paradigm may have a kindling (i.e., seizure-inducing) effect in the long-term. However, this phenomenon has yet to be rigorously evaluated because follow-up data beyond five years for the RNS trial have yet to be published.

Another area of future research will be aimed at determining which candidates are optimally suited to ATN stimulation. In the SANTE trial, patients with seizures of temporal origin experienced a median seizure reduction of 44.2%, whereas patients with frontal, parietal, occipital, multifocal, or diffuse-origin seizures did not experience comparable benefit. These results suggest that patients with temporal lobe epilepsy may be the best candidates for ATN DBS. Results from the RNS trial indicate that patients with bilateral hippocampal foci may be the ideal candidates for RNS [79]. However, further work will be needed to optimize patient selection for these treatments.

SUMMARY

Deep brain stimulation for the treatment of epilepsy holds promise for the treatment of patients with medically refractory epilepsy. Data from randomized clinical trials for ATN DBS and RNS of seizure foci support this statement, as do numerous smaller uncontrolled studies. Responsive neurostimulation is now FDA approved, and ATN DBS may be approved in the near future. In addition, other targets, including the hippocampus and CM-Pf thalamic nuclei, may hold promise for the treatment of epilepsy.

Ultimately, however, determining optimal stimulation parameters and candidates is hindered by our lack of understanding of the mechanisms by which DBS is able to abort seizures. Pioneering optogenetic studies of animals have begun to identify the networks responsible for epileptogenic activity and the results of these studies will help in the development of novel closed-loop techniques for aborting seizures [85, 86]. Studies such as these will likely deepen our understanding of epilepsy and of the therapeutic

mechanisms of neurostimulation, and improve outcomes. The coming decades undoubtedly hold exciting advances in this field that will impact basic science and clinical care for individuals with medically refractory epilepsy.

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Chapter 14

Deep Brain Stimulation for Memory Dysfunction

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INTRODUCTION

DBS has recently been introduced as a potential treatment to address memory dysfunction associated with Alzheimer's disease (AD) and Parkinson's disease (PD). This possibility was first considered following DBS surgery for morbid obesity in a single patient, during which stimulation of the hypothalamus resulted in unexpected stimulation-evoked memory recall [1]. Given the proximity of the hypothalamus to the fornix, an important structure for memory storage and retrieval, it was hypothesized that the current spread to this structure was responsible for the recall phenomenon. Based on this initial finding, a preliminary safety study was conducted investigating fornix DBS in six patients with mild AD [2], and it was found that they experienced significant slowing in cognitive decline without serious adverse effects. Since then, several clinical studies have contributed to the idea that

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DBS for memory enhancement may have potential for slowing the progression of memory loss in both AD and PD [2–4]. These studies and the rationale for targeting the fornix and other structures important to memory in the Papez circuit will be discussed in greater detail in this chapter.

Neuroanatomy: The Papez Circuit

DBS for memory enhancement has focused on structures that play key roles in memory encoding and retrieval. Several structures within the Papez circuit are of interest, including regions of the medial temporal lobe (MTL), specifically, the hippocampus, entorhinal cortex, and perirhinal cortex. The Papez circuit consists of the hippocampus, fornix, mammillary body, anterior nucleus of the thalamus, cingulate cortex, parahippocampal gyrus, and entorhinal cortex [5]. As seen in Fig. 14.1, it

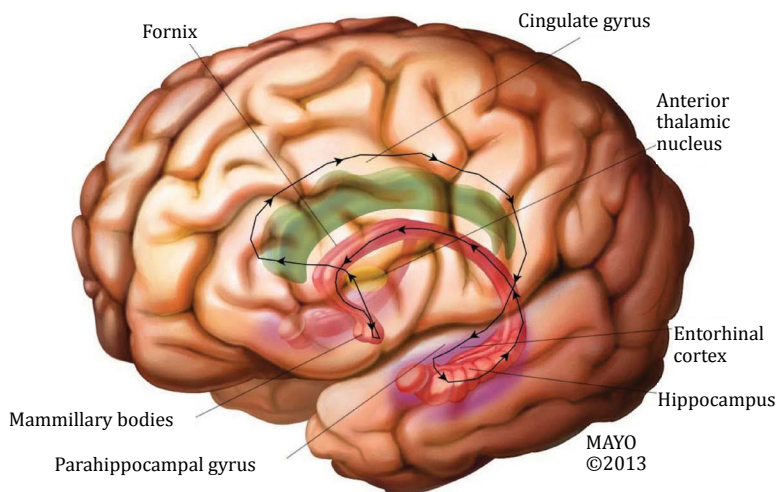


Figure 14.1 The Papez Circuit. Fibers project from the hippocampal formation through the ascending fibers of the fimbria before branching out into bilateral projections through the fornix. These fibers terminate in the ipsilateral mammillary body. From there, the tract continues up through the mammillothalamic tract to the anterior nucleus of the thalamus. It then ascends through the cingulate gyrus and moving posterior and inferior, through the parahippocampal gyrus, entorhinal cortex, and terminating back in the hippocampal formation.

begins at the hippocampal formation, with fibers projecting from it along the white matter tract of the fimbria/fornix, continuing through the fornix body, and terminating in the ipsilateral mammillary body. The circuit continues via the mamillothalamic tract, which enters the anterior nucleus of the thalamus. The anterior fibers continue forward and enter the cingulate gyrus. Projections travel through the cingulate gyrus, then continue through the parahippocampal gyrus, enter the entorhinal cortex, and end at the hippocampus, completing the circuit [6, 7]. Structures in this circuit play a major role in learning, memory, and emotional processing while dysfunction in the Papez circuit is associated with neurological and psychiatric diseases such as AD, schizophrenia, and epilepsy [8–11].

Pathophysiology

Dementia is characterized by progressive impairment in memory, executive functions (reasoning, judgment, impulse control), perception, and/or language. Although it is associated most often with AD, progressive, irreversible dementia is a major symptom in certain neurodegenerative conditions including, Lewy-body dementia, frontotemporal dementia, and Huntington's disease. Vascular dementia, the second most common form of dementia, results from insufficient blood flow to the brain from stroke or other vascular conditions. Dementia can also be associated with head trauma, movement disorders (such as PD), and neuromuscular disorders.

In 2010 the worldwide cost of dementia was estimated at \$604 billion, a cost that is projected to increase dramatically as the time between diagnosis and treatment is reduced and life expectancy increases [12, 13]. AD is the most common form of irreversible dementia, with the number of projected cases estimated at 81.1 million by 2040 [12]. It is also the sixth leading cause of death in the U.S., and although it typically appears after age 65, up to 5% of patients have an “early onset” form of AD in which the symptoms occur at 40 to 50 years of age [14].

While the symptoms of AD can progress to include changes in mood, behavior, personality, speech, and language comprehension, as well as produce hallucinations, delusions, and motor incoordination, the clinical hallmark of AD is impaired

memory. Memory takes many forms and depends on learning, consolidation, and storage as well as on recall. The specific type of memory at risk early on in AD is declarative or episodic memory, that is, the recall of events and facts [15]. The MTL is the primary site of cortical atrophy in AD [16–18], and abnormalities observed in the fornix using magnetic resonance imaging (MRI) may predict decline in memory function [19].

AD is considered a multifactorial disease involving an array of identified pathological processes, including amyloid- β ($A\beta$) pathology, neurofibrillary tangle deposition, and region-specific metabolic dysfunction (Fig. 14.2) [20, 21]. A pathophysiological diagnosis of AD can only be made post-mortem when neocortical neuritic plaques and neurofibrillary tangles are observed [20, 22].

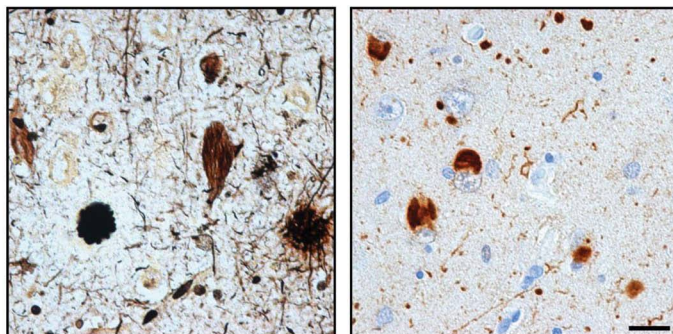


Figure 14.2 AD and PDD pathology. AD case in left panel shows $A\beta$ plaques and tau neurofibrillary tangles labeled with a Bielschowsky silver stain. PDD case in right panel shows Lewy neurites labeled by α -synuclein immunohistochemistry. Scale bar = 20 μ m.

Neurofibrillary tangles are made up of abnormally phosphorylated microtubule-associated protein tau within a subset of neurons. Synaptic loss associated with AD is correlated with the accumulation of these two key molecular abnormalities [23, 24]. Disruption in the MTL and other cortical regions associated with memory storage and retrieval, called the default network, has been shown to occur with cognitive deficits and episodic memory loss in AD [16, 25, 26]. These processes are thought to interplay, causing a progressive cascade, in which network function is disturbed beginning at a molecular level (Fig. 14.3a) [21, 27]. These molecular changes affect neurons

at the circuit level and ultimately at the level of the default neuronal network (Fig. 14.3b) [16, 25, 26]. Available treatments for AD include cholinesterase inhibitors and NMDA receptor antagonists that attempt to ameliorate these pathologies, but they provide only nominal symptom improvement and do not prevent disease progression [28]. Moreover, in addition to memory loss, neuropsychiatric symptoms such as depression, apathy, and agitation occur in more than 98% of patients with AD [21, 29].

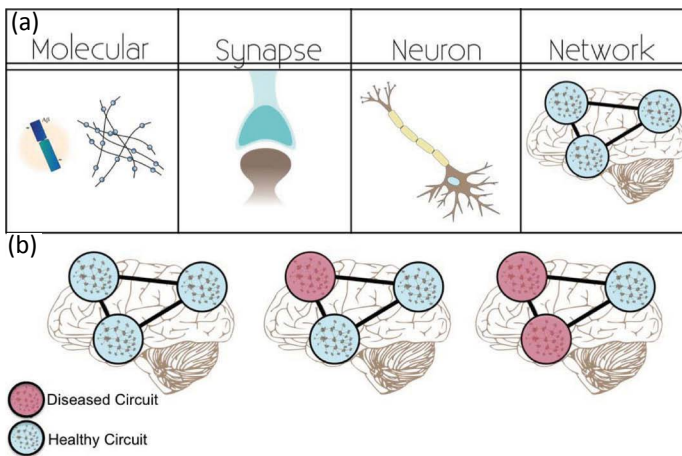


Figure 14.3 Molecular to circuit dysfunction. (a) Molecular changes including pathogenic amyloid- β plaques and tau neurofibrillary tangles cause synaptic-level disruption and cell death resulting in circuit-level disruption and ultimately network-level dysfunction. (b) Molecular changes that affect neurons at the network level will eventually affect neurons on a circuit level, resulting in circuit dysfunction.

PD is the second most prevalent neurodegenerative disease. It is characterized by a progressive loss of dopaminergic neurons beginning in the substantia nigra and leading to neuronal loss within the interconnected dopaminergic circuits. In addition to its well-characterized motor abnormalities, there are several non-motor symptoms associated with PD, including memory deficits. Approximately 40% of patients with PD develop comorbid dementia [30–32] known as Parkinson’s disease dementia (PDD; Fig. 14.2). This disorder is similar in pathophysiology to dementia with Lewy bodies (DLB), despite differences in their clinical course [33]. Cortical and striatal α -synuclein inclusions occur

in both PDD and DLB (Fig. 14.3) and are found more widespread in these disorders than in PD without dementia [34].

Although the proposed mechanisms underlying dementia in PD and AD are quite different, similar pharmacological therapies are used to treat the memory deficits associated with both diseases [35]. In both conditions the boundaries of neuronal loss provide a potential, albeit variable, therapeutic target at the level of the surviving neuronal population (Fig. 14.3b). Therefore, modulating the surviving neuronal networks by DBS may provide global reinforcement of the healthy and compensatory circuits that remain unaffected by neurodegeneration-induced cell loss. With an increasing number of patients suffering from memory loss and the urgent call for effective therapy, several groups have investigated the potential of DBS as a treatment for memory loss associated with AD and PD [2–4].

CLINICAL DBS TARGETS

Fornix

Within the Papez circuit, the fornix plays an integral role in episodic memory, and it has recently become a target for AD-associated memory loss (Fig. 14.4). It is the major white matter tract connecting the two brain regions that are most consistently associated with episodic memory deficit: the MTL and the medial diencephalon. Several studies have shown that lesions of the fornix cause episodic memory deficits in humans and episodic-like memory deficits in animals, supporting this pertinent role of the fornix in memory function [36–38].

The discovery that fornix DBS enhanced episodic memory was reported in 2008 by Hamani and colleagues, who found that a 50-year-old male patient with chronic, treatment-resistant obesity, undergoing bilateral hypothalamic DBS to treat his eating disorder, reported vivid moments of episodic recall intraoperatively during ventral contact stimulation (3–5 V, 130 Hz, and 0.60 ms pulse width). This contact site was found to align well with the fornix, and the authors hypothesized that the patient's recall was due to current spread into this structure. Following surgery, the patient's scores on a variety of memory recall and learning tests increased by one and a half standard deviations.

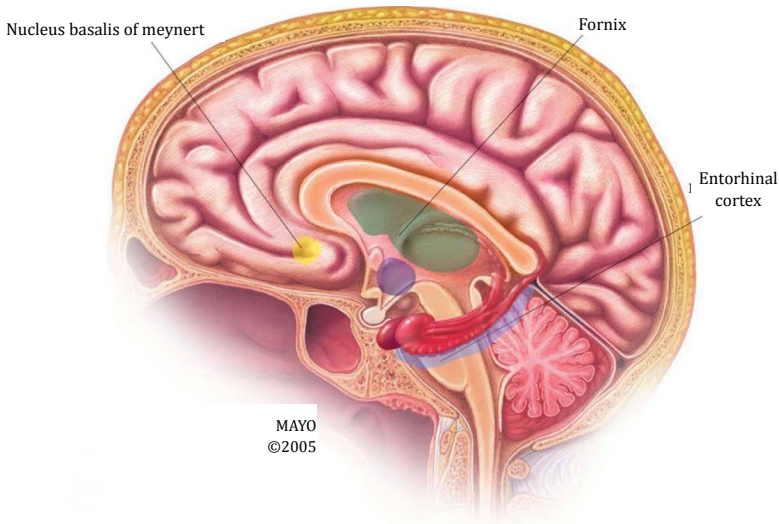


Figure 14.4 Clinical DBS targets for memory loss. The three effective clinical targets for memory disorders include the nucleus basalis of Meynert, the fornix, and the entorhinal cortex.

Based on this single case, six patients with early AD were enrolled in an early feasibility study of bilateral fornix stimulation [2]. The DBS quadripolar electrode (Medtronic 3387) was positioned 2 mm anterior and parallel to the fornix within the hypothalamus. To investigate potential circuitry involvement, several imaging techniques were used at the beginning and end of the one-year study. Initially, using standardized low-resolution electromagnetic tomography (sLORETA) the investigators found that brief fornix stimulation resulted in a latent and significant activation in the ipsilateral hippocampus, parahippocampal gyrus, and cingulate gyrus. Additionally, sustained increases in glucose metabolism were observed in the temporoparietal regions relative to the preoperative metabolic decreases characteristic of AD [2]. In a more comprehensive study, a second cohort of six affected individuals were enrolled and received continuous fornix stimulation (3–3.5 V, 130 Hz, 90 μ s pulse width) for one year. At the end of the year, the patient average showed increased glucose metabolism in cortical-hippocampal and cortical-subcortical networks. This physiologic effect directly correlated with significant improvement in the group average on tests of cognition, memory, and quality of life [3].

There are now several ongoing clinical trials that are further assessing the application of fornix DBS for AD. The largest of these is a double-blind, randomized controlled feasibility study of 50 patients with probable mild AD [39]. The study is not yet complete, but the results are highly anticipated as it will be the first case-controlled randomized study investigating fornix DBS for AD.

Nucleus Basalis of Meynert

Cholinergic neurons in the nucleus basalis of Meynert (NBM) degenerate in AD as well as in PDD, and neuronal loss is associated with memory loss [40, 41]. To address the memory decline in AD and PDD at the level of the NBM, several groups are investigating the effects of DBS in this structure (Fig. 14.4). The initial case report involved a 74-year-old man with probable mild to moderate AD which was pathologically confirmed [42]. The patient failed to demonstrate improvement in cognition eight months after the surgery. However, the technique has evolved a great deal since this initial 1985 study so despite this disappointing initial finding, the NBM remains a DBS target of interest for AD [43]. In the first clinical investigation, six patients with mild to moderate AD received bilateral low-frequency NBM DBS [43]. The outcome measures for this four-week double-blind, sham-controlled clinical trial and the 11-month follow-up were the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and PET imaging. Four of the six patients were considered responders, defined as stable or improved primary outcome parameters, when they were assessed 12 months after the surgery.

NBM DBS has also been applied in a 71-year-old male patient who's clinical presentation fit the clinical diagnostic criteria for PDD [44]. The patient had a 22-year history of PD and a two-year history of declining memory, knowledge acquisition, mental processing speed, executive function, concentration, and praxis. The results of 10 weeks of NBM stimulation (1 V, 20 Hz, 0.120 ms pulse width) showed a positive effect, though not significant, on cognitive function and memory as measured by the Auditory Verbal Learning and Memory Test (AVLT) [45]. Although the results to date for NBM DBS as a treatment for AD and PPD are mixed, the positive effects in some cases suggest it may be a valid target for further investigation.

Entorhinal Cortex

The entorhinal cortex, which projects directly to the hippocampus and is part of the Papez circuit (Figs. 14.1 and 14.4) [46], has been suggested as an alternative to the fornix for treating memory deficits associated with AD and PDD. Recently, six patients with medically refractive epilepsy underwent DBS in the entorhinal cortex. Four of the six had had additional hippocampal electrode implantation. This study revealed that anterior entorhinal stimulation during a spatial navigation task increased learning efficiency compared to exclusive hippocampal stimulation or lack of stimulation [4]. These findings suggest that entorhinal stimulation may also have a positive effect on Papez circuit function and that it may have potential to improve certain aspects of learning and memory in the context of disease.

POSSIBLE MECHANISMS OF ACTION

Although its mechanisms are poorly understood, several studies suggest that DBS within various regions of the Papez circuit and within the cholinergic NBM may activate neurons in undamaged portions of the remaining neural memory circuitry in the context of neurodegeneration, prevent a reduction in glucose metabolism, and lead to hippocampal neurogenesis [2–4]. Current DBS theories suggest that by acting on neural circuits, high-frequency stimulation inhibits or excites specific brain regions. One theory suggests that DBS for memory may enhance innate electrophysiological patterns that underlie long-term memory encoding and retrieval within the MTL [47]. This potential mechanism suggests that DBS in the MTL must be individualized and that stimulation parameters are particularly important because DBS primarily exerts an effect on extracellular field-potential oscillations. This may be the mechanism by which DBS prevents pathogenic degeneration, at least temporarily.

Several animal models have been used to investigate the mechanisms that explain the potential effects of DBS. In one investigation of a drug-induced animal model of AD, Sprague Dawley rats received bilateral stimulation in an area close to the fornix, which was found to alleviate spatial memory impairment without significant adverse motor or behavioral effects [48].

To further understand the neural circuitry mechanisms of fornix DBS, functional imaging has been used in a swine model of DBS to monitor the blood oxygen level-dependent (BOLD) changes with stimulation [49–51]. As Fig. 14.5 shows, there were significant changes within hippocampal circuitry, including structures of the hippocampus, entorhinal cortex, and parahippocampal gyrus ($FDR < 0.001$). This study supports the concept that patterns of stimulation-evoked BOLD activation occur in areas of the MTL and Papez circuit with fornix DBS.

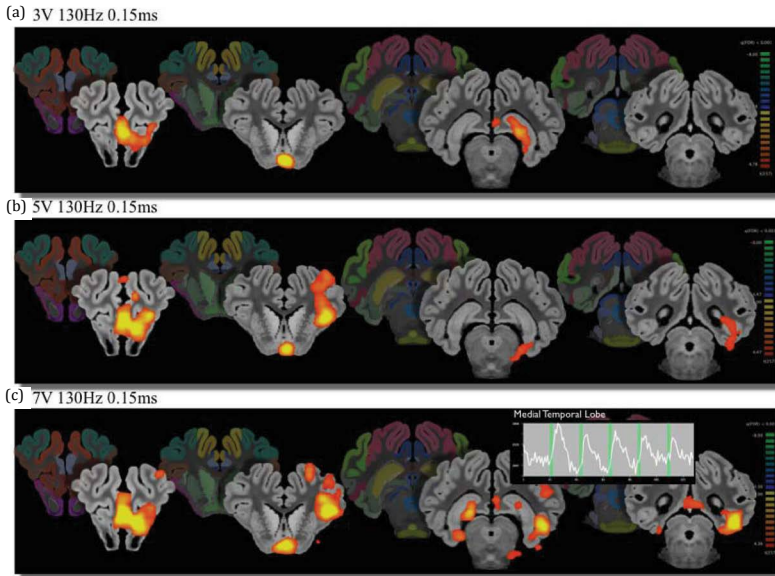


Figure 14.5 Potential mechanism of fornix DBS: fMRI large animal studies. Coronal plane images of areas of activation in fornix stimulation under different amplitude parameters, normalized to a 3D pig brain template [53]. (a) Stimulation at 3 V 130 Hz 0.15 ms resulted in activation in the ipsilateral prefrontal cortex, hippocampus, and nucleus accumbens. (b) Stimulation at 5 V 130 Hz 0.15 ms resulted in the activation in the ipsilateral prefrontal cortex, insular cortex, nucleus accumbens, the medial temporal lobe, and decreased hippocampal activation. (c) Stimulation at 7 V 130 Hz 0.15 ms resulted in the activation in the ipsilateral prefrontal cortex, insular cortex, nucleus accumbens, hippocampus, and both ipsilateral and contralateral activation in the medial temporal lobe.

It may also be that DBS stimulates neurogenesis. For example, a recent study of mechanisms of entorhinal cortex DBS in mice demonstrated that six weeks post-stimulation there were transient increases in adult dentate gyrus neurogenesis and increased synaptic function in the existing hippocampal network, concomitant with increased scores in tests of spatial learning memory [52]. It is unknown if stimulation to other regions of the Papez circuit could produce the same effect.

LIMITATIONS OF DBS FOR MEMORY ENHANCEMENT

DBS for AD and PDD is limited by certain unaddressed pathophysiological variables, such as $A\beta$ plaques and tau tangles in AD and α -synuclein pathology in PDD. Little is known about the relationship between these molecular pathologies and DBS [54]. The importance of identifying the correct anatomical target for modulating relevant circuitry in AD and PDD cannot be over-emphasized. A recent study of male Wistar rats, for example, found that high amplitude DBS of the anterior nucleus of the thalamus resulted in an impaired fear response, considered a measure of episodic memory. This finding both reinforces the role of this Papez circuit structure in memory and reveals that not all targeted structures are appropriate [1]. Although DBS may not act directly at the level of the characterized molecular lesions in AD and PDD, studies suggest that there can be a positive effect, and that it may be due to widespread memory network activation. However, the clinical studies of DBS for AD and PDD have been very superficial, and until more comprehensive and extensive studies are conducted, it is difficult to draw conclusions regarding the therapeutic effect of DBS for memory.

SUMMARY

Memory impairment is a major global health concern with rising economic and social costs, and there is a critical need for the development of effective treatments to slow or stop disease progression. The studies discussed in this chapter suggest that DBS is capable of affecting neuronal activity within the pathologic

circuits associated with memory loss and may produce positive outcomes in cognitive function. The three clinical targets investigated to date include the fornix to treat AD, NBM for AD and PDD, and entorhinal cortex for AD. Additional targets that have been suggested include several structures within the Papez circuit, such as the anterior thalamic nucleus, the mammillothalamic tract, and the hippocampus.

Although the application of DBS for memory dysfunction is expanding, there are many issues left to consider, including several ethical questions that need to be addressed, such as patient consent in the context of cognitive decline. The initial clinical case studies and animal model investigations reported here highlight the importance of ensuring that both targets and stimulation parameters are chosen carefully. Collectively, these reports suggest that DBS used to treat dementia deserves further comprehensive clinical and molecular investigation.

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Chapter 15

Deep Brain Stimulation for Cluster Headache

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INTRODUCTION

Cluster headache (CH) is a primary headache disorder which is designated as a trigeminal autonomic cephalgia (TAC) by the International Headache Society classifications [1]. It is considered one of the most disabling of all headache types and has a population prevalence of one case per 500 people [2]. Fortunately most patients have an episodic form of the disorder and up to 27% of patients have only a single cluster event. However, according to the Headache Classification Committee of the IHS [1], 10–15% of patients with CH have chronic cluster headache without apparent remission between attacks. For those patients, the pain and disability associated with CH can be so severe that suicide is often contemplated [3].

Neuromodulation in the form of deep brain stimulation (DBS) is one of the emerging therapeutic options to rescue

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patients with chronic CH (CCH) who are refractory to standard treatments. The past 15 years have seen the investigational use of DBS for this select group of these patients, with approximately 50 published cases worldwide. This chapter reviews the characteristics of CH, conventional treatment of CH, and the patient selection, surgical approach, outcomes, and complications of DBS for CCH.

OVERVIEW OF CLUSTER HEADACHE

Cluster headache is defined as a severe unilateral headache that is centered on the orbit, supraorbital or temporal regions of the head and lasting from 15 to 180 min. In the episodic form, they occur in clusters of attacks, hence the name. Attacks can occur every other day and sometimes as often as eight times a day. CH is associated with autonomic nervous system symptoms on the side of the headache pain, which can include: ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, forehead or facial hydrosis, miosis, or ptosis, and a general sense of restlessness [1].

The prevalence of CH is about 1/1000 people independent of region [4]. The disease substantially impacts quality of life even when adequately treated [5]. There is a male predominance (3:1), and the disorder has been correlated with smoking [6]. The majority of patients have episodic CH (ECH) but one out of seven patients with CH may present with or develop CCH, which is defined as CH attacks for more than a year with remission of one month or less.

CH has a striking circadian and circannual periodicity. Patients often have attacks at the same time of the day and same time of the year. Because of this periodic nature, the pathophysiology of CH is thought to be related to the hypothalamus, and diagnostic work-up should rule out pituitary gland pathology [7]. Treatment for CH includes prophylactic and abortive medications which can provide relief to the majority of patients. One of the fastest and most effective treatments is high-flow oxygen of at least 7 L/min. High-flow oxygen is a relatively safe treatment and inhalation through a proper fitting mask while sitting upright is recommended. The therapy is usually 20 min in duration, and up to 60% of patients report it to be efficacious [8].

However, the disadvantage of oxygen therapy is the need of a supply of oxygen and a mask.

ECH patients often need intermittent prophylactic medication in addition to abortive medications. The most commonly used first-line agent is verapamil, sometimes at very high doses. Lithium appears to have a relatively similar efficacy profile, but the narrow therapeutic window and frequent laboratory monitoring makes it less useful as a first line agent. In addition, Methysergide and corticosteroids are also used [9]. For CCH patients, however, maintenance prophylaxis and even multiple agents may often not be adequate. Surgical or gamma knife lesioning of the trigeminal nerve has been tried but leaves patients with facial paresthesia, and the morbidity of the procedures may not be justified by the low response rate [10, 11].

DEEP BRAIN STIMULATION FOR CHRONIC CLUSTER HEADACHE

DBS of the posterior inferior hypothalamus has been shown to be effective in a small sample of patients with intractable and drug resistant CCH [12]. As discussed above, the circadian periodicity and the hormonal findings seen in some CH patients strongly suggested a role of the hypothalamus in the pathophysiology of CH [13]. The ipsilateral hypothalamic gray matter identified in studies of positron emission tomography (PET) and voxel-based-morphometry magnetic resonance imaging (MRI) has led to the theory that this site is at least partly the generator of CH [7, 14]. For these reasons, this region has become the target of choice for DBS treatment of CH [15].

Patient Selection for DBS

To date, there have been about 56 cases reported in the literature of patients who have undergone DBS for CCH. Based on international consensus statements, all of them have tried all first-line therapies and often other procedures, which have failed either because of the lack of therapeutic effect or due to intolerable adverse effects [16]. Research at Fondazione IRCCS Istituto Nazionale Neurologico Carlo Besta in Milan, led by Massimo Leone, has the

largest series to date (19 subjects). He and his colleagues have published proposed guidelines for patient selection [3]. They suggest that candidates must have intractable CCH and not ECH and that the CCH should be of at least 2-year duration with daily or almost daily attacks. This time-frame allows for trials of standard available CH prophylactic medications. Further recommendations are listed in Table 15.1.

Table 15.1 Criteria for electrode implants

1. CCH diagnosed according to IHS criteria
2. Attacks must be strictly unilateral
3. Attacks must be documented either during hospitalization or on video
4. All conventional drugs for CH prophylaxis must have been tried in sufficient dosages alone or in combination, where applicable
5. Normal psychological profile
6. No medical/neurological conditions contraindicating surgery
7. Normal neurological examination except for symptoms characteristic of CH
8. Normal CT scan and cerebral MRI, including cranio-cervical transition and MRI arterial and venous angiography
9. Neurosurgical team experienced at performing stereotactic implant of electrodes
10. Patient is not pregnant
11. Ethics committee/IRB approval
12. Patient gives up smoking and drinking alcohol
13. Patient informed and gives written consent

Source: Adapted from [3].

Surgical Technique for DBS

The surgical approach for CCH is similar to that for other DBS surgeries with targeting conducted by MRI-based stereotaxy. The posterior hypothalamus is the target of choice for CCH based on functional imaging work and melatonin levels showing differential activity in this region in CH patients [7, 17]. Although ventroposterolateral/ventroposteromedial (VPL/VPM), periacqueductal gray

(PAG), and periventricular gray (PVG) are used for nociceptive and neuropathic pain, respectively, these sites are not specifically used as targets for CH [18].

Following surgery, monopolar stimulation at a pulse width of 60 μ s, frequency of 130–185 Hz, and voltage up to 7 V has been used. However, amplitudes above 4 V usually produced lateroversion of the ipsilateral eye toward the stimulated side resulting in diplopia, so the standard voltage is typically less than 3 V [12]. It is recommended that stimulation be initiated after the patient has had a spontaneous CH, and it appears that constant, long-term stimulation is required for clinical benefit [3]. Sillay et al. [15] proposed a modification in the programming algorithm used by Franzini et al. [19] and Schoenen et al. [20].

Clinical Outcomes

A survey of the literature by Pedersen found that of 56 implanted patients, there was an average of >50% percent improvement in 67% of the patients [21]. The 19 patients reported by the study led by Massimo Leone had one of the best outcomes with an observed maintenance of improvement in 12/17 (71%) of patients at a mean follow-up of 8.7 years. Six of the 12 patients reporting relief were almost pain free. The other six had switched to an ECH pattern. Five patients were pain free even after stimulation was turned off, but this only occurred after several years of continuous stimulation. In some patients whose battery ran out or in whom the electrode had dislodged, the headaches returned. Five patients had no significant long-term benefit from DBS. Three patients reported a 1–2-year period of positive response before developing tolerance. Four of the five patients who did not respond well to the treatment had bilateral disease, which suggests that bilateral CH might be predictive of poor DBS outcomes.

Two other groups using the same target achieved an efficacy of only 50% [21]. However, as reported in the Milan group follow-up data, stimulation effects were not experienced for an average of 2–16 weeks, and other studies reviewed by Pedersen also found a delay (weeks to months) for therapeutic benefit. It should be noted that posterior hypothalamus stimulation has also been tried as a CH abortive therapy but without clear effect. Thus, the use of

DBS is restricted to chronic cases and is not considered an acute headache treatment.

Complications

It appears that hypothalamic DBS implantation is well tolerated. Like invasive surgery, this does pose a risk of hemorrhage, infection, and other complications. Adverse post-surgical effects specific to CCH DBS include oculomotor disturbances and vertigo. Mood changes have been reported during implantation. In two reported cases, patients suffered panic attacks and one operation had to be aborted [20, 22]. Transient ischemic attack, infection, micturition syncope [23], erectile dysfunction, and paroxysmal sneezing also have been reported with hypothalamic DBS [21]. There is improvement in sleep structure, possibly due to decrease of nocturnal CH attacks [21].

CONCLUSION

CH is a devastating primary headache disorder, so much so that it is often been referred to as a “suicide headache” disorder. While most patients have episodic CH, a sub-population of these patients develops or presents with chronic CH, which can be medically intractable. There are few well-tested medications, especially maintenance prophylactic medications that do not have adverse effects. The circadian nature of CH led to identification by PET and MRI of the posterior hypothalamic region as a possible target for DBS. So far there have been only 56 published cases on DBS in the hypothalamus for CCH, and the average benefit has been found to be approximately 67% [21]. Overall the procedure seems to be well-tolerated long-term with mild adverse effects. The fact that in some cases, several years of chronic stimulation led to remission of CCH after stimulation was ceased suggests that neuroplasticity may be a factor in the efficacy of DBS for CCH. There is still very little data on which patient characteristics predict best outcome. The recent results from occipital nerve stimulation (ONS) for chronic CH also seem to show a similar efficacy of 67% [24]. Whether there is a role for a trial of ONS, which may be safer prior to DBS, is not clear.

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Chapter 16

Functional Electrical Stimulation for the Treatment of Spinal Cord Injury

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INTRODUCTION

Spinal cord injury (SCI) is a complex and devastating condition involving permanent disruption of signal transmission between the brain and the sensorimotor and autonomic systems below the injury level. This disruption is typically caused by vertebral bone and disc fragments, dislodged by fractures and dislocations, that puncture or rupture neural tissue and blood vessels [1].

The American Spinal Injury Association (ASIA) has established a clinical diagnostic scale that divides SCI into five categories (ASIA A, B, C, D, and E), depending on the degree of neurological deficit [2]. The category descriptions are as follows: **ASIA A:** no sensory or motor function in the fourth and fifth sacral (S4, S5) spinal segments; **ASIA B:** preservation of sensory function below the level of injury, including the fourth and fifth sacral

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spinal region, but absence of motor function more than three spinal levels below the injury; **ASIA C** and **D**: intact sensory function and motor function more than three spinal levels below the injury, the difference between them depending on the degree of motor activity that is present, which can range from palpable muscle contractions to either observable or functional limb movement; and **ASIA E**: complete recovery of motor and sensory function.

It is estimated that in the United States alone, with an annual incidence of 40 cases per million, 240,000 to 337,000 people live with paralysis resulting from SCI [3–5]. The majority of these cases are caused by vehicular accidents (38%), falls (30%), violence (14%), and sport injuries (9%) [5]. Mortality rates associated with SCI have drastically decreased in the last 30 years due to improved emergency responsiveness, surgical stabilization, and early post-injury rehabilitation strategies [6]. Improved prevention and treatment of secondary complications (e.g., urologic infections, renal failure, and respiratory complications) has further reduced mortality rates and continues to drive the average life expectancy of SCI victims toward that of the general population [3, 7–9]. However, metabolic changes, autonomic dysfunction, and reduced physical exercise leading to loss of muscle mass and increased levels of adipose tissue increase the risk of cardiovascular complications for SCI survivors [10–13]. Thus, risk of premature death in SCI survivors continues to be higher than in individuals without SCI [14–16]. These health-related complications, combined with an estimated patient population cost of over \$35 billion annually in the United States, highlight the importance of improving current therapies and restoring function lost as a result of SCI [5].

FUNCTIONAL ELECTRICAL STIMULATION

Limb movement as well as the autonomic functions of respiration, bladder, bowel, and sexual function receive inputs from higher brain centers, but are ultimately controlled by efferent neurons that originate within the grey matter of the spinal cord [17]. When transmission of brain signals to these efferent neurons are interrupted, permanent loss of motor and autonomic function

occurs below the lesion. However, the spinal circuitry both above and below the injury remains intact. These intact neuromuscular networks lay dormant but remain capable of evoking and coordinating limb movements when externally stimulated [18–22]. This can be achieved using functional electrical stimulation (FES), a form of therapy that applies electrical currents to various locations within the neuromuscular networks below the level of injury to evoke muscle contractions (Fig. 16.1) [23]. Electrical excitation of motor neurons leads to depolarization of skeletal muscle, followed by a cascade of events within the myocytes, which results in contraction of the muscle and thus a “functional” response (Fig. 16.2).

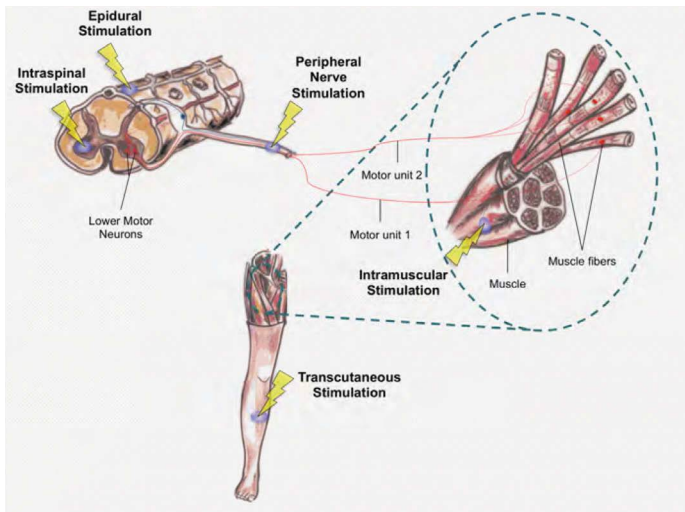


Figure 16.1 Functional electrical stimulation techniques. Various electrical stimulation modalities can be used to restore motor function following spinal cord injury. Electrical stimulation of the epidural surface of the spinal cord activates dormant circuitry below the level of injury and allows restoration of function. Intraspinal stimulation of spinal circuitry within motor centers of the ventral horn can activate synergistic muscle groups to restore motor function. Peripheral nerve stimulation can directly activate motor units, leading to muscle contraction. Intramuscular stimulation can directly activate muscle fibers within target muscles. Transcutaneous stimulation provides generalized activation of muscles near the site of stimulation.

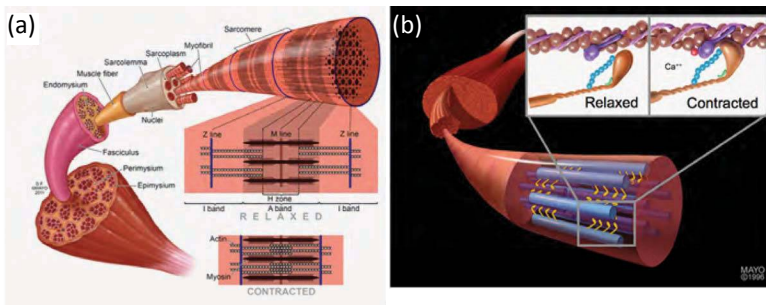


Figure 16.2 Skeletal muscle structure and contraction. (a) Cross-sectional representation of the levels of organization within skeletal muscle (left). The components within a sarcomere, the basic unit of muscle tissue, are shown during relaxation and contraction (right). During contraction, the A-bands remain unchanged while the I-bands and H-zone shorten causing the Z lines to contract. (b) Illustration of muscle contraction at a molecular level. During relaxation the protein tropomyosin (light purple) covers the myosin binding sites of the actin molecules (brown upper chain) impeding contraction. In order to allow muscle contraction, calcium (red sphere) is released from the sarcoplasmic reticulum and binds to troponin-C (dark purple), causing tropomyosin to shift, revealing the myosin-binding site on actin. Myosin (lower brown colored structure) then binds to actin resulting in muscle contraction. (Adapted and reproduced with permission from Mayo Clinic).

Nerve fibers, or motor units, are recruited in a specific order. According to Henneman's size principle, muscle fibers are recruited from the smallest (low-force, fatigue-resistant) to the largest (high-force, easily-fatigued) [24]. By minimizing overall muscle fatigue, this recruitment order allows movement to occur over long periods of time. However, when extracellular stimulation is applied, as it is in FES, the recruitment order is reversed due to the intrinsic properties of neurons, which follow classical cable theory [25]. Cable theory states that axon diameter is inversely proportional to membrane resistance and proportional to membrane capacitance [25]. As a result, increased ionic flow across the membrane and subsequent membrane depolarization causes large myelinated fibers near the stimulating electrode to become activated first [26, 27]. Thus, extracellular electrical

stimulation results in patterns of muscle fiber activation that significantly increase metabolic energy expenditure, leading to muscle fatigue and suboptimal recovery of function. Despite these suboptimal activation patterns, clinical research has shown that FES can restore a variety of functions following SCI (Fig. 16.3). However, as described in the following sections, whether strictly investigational or applied clinically, FES systems are not without technological limitations. Research is focused on solving these problems precisely because of the great potential FES holds for restoring independence and improving health in the SCI population.

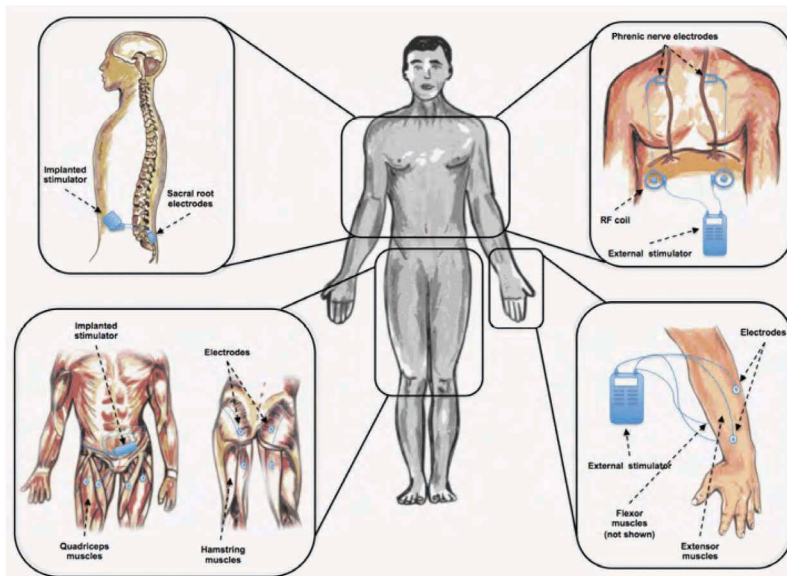


Figure 16.3 Functional electrical stimulation systems. Multiple types of functional electrical stimulation systems have been used for restoring motor function following spinal cord injury. Clockwise from the upper left panel, examples include: a sacral anterior nerve root stimulation system for controlling urologic function (upper left); a phrenic nerve stimulator to restore diaphragm function (upper right); a transcutaneous stimulation system for controlling hand grasp and release via activation of flexor and extensor muscles of the forearm and hand (lower right); and a multi-channel implantable system for stimulating lower limb muscles (lower left).

FES system designs can be classified according to the location of the stimulation (e.g., transcutaneous, intramuscular, peripheral nerve, or spinal epidural) and whether the system is implanted or external. The most common functions restored via these systems include standing [28, 29], stepping [30, 31], seated posture [32], hand grasp [33, 34], bladder control [35, 36], and respiration [37, 38].

Transcutaneous Electrical Stimulation

Transcutaneous stimulation consists of placing stimulating electrodes on the skin surface directly over anatomical locations that provide a balance between maximum contraction strength and minimum stimulation amplitude [39–41]. This technique is one of the most commonly used forms of FES in the rehabilitation setting because it represents a noninvasive, reversible, and inexpensive way to improve and maintain health following SCI [42, 43]. Transcutaneous FES can significantly improve muscle strength [44] and has been associated with improved cardiovascular function [11, 13], and thus improved blood glucose metabolism [45] and, when combined with dietary intervention, improved lipid profiles [46, 47]. Additionally, FES-driven cycling has been reported to decrease bone resorption rates and improve bone density, thereby decreasing the risk of osteoporosis and fractures [48–53]. Transcutaneous FES also has been shown to improve self image [54] and mood [55].

Unfortunately, donning and doffing transcutaneous stimulation systems is difficult, which increases dependence on caregiver assistance. In addition, the spread of electrical currents through tissue is not well constrained, and thus, selective activation of specific nerves and muscles is not always possible. Finally, transcutaneous stimulation can lead to activation of sensory fibers, which may trigger pain sensation in individuals with ASIA B, C, and D injuries. However, it is worth noting that recently Gerasimenko and colleagues reported a novel stimulation paradigm that suppressed sensory fiber activation while simultaneously activating spinal motor circuitry via transcutaneous stimulation [56]. They found that transcutaneous stimulation applied to multiple sites along the spine of neurologically intact subjects

resulted in initiation and modulation of locomotor-like movements [56]. This finding suggests that development of transcutaneous paradigms as a means of restoring motor function in SCI survivors warrants continued investigation.

Implantable Peripheral Electrical Stimulation

Implantable FES systems rely on the application of electrical currents directly to the muscles or to peripheral nerves [57–61]. Muscle stimulation can be applied either near the motor endplate region (intramuscular stimulation) or in proximity to the innervation point at the muscle surface (epimysial stimulation) [62]. Intramuscular FES systems have been developed to control upper and lower limb function. For example, restoration of hand grasp has been coupled with stimulation-evoked upper arm control to allow hand-to-mouth activities [58]. Implantable intramuscular FES systems also have been used to improve seating balance, posture, and gait in individuals with lower limb paralysis [31, 32, 63, 64].

Another form of implantable FES is direct stimulation of peripheral nerves via nerve cuff electrodes that surround the nerves innervating target muscles [59–61]. Peripheral nerve stimulation has several distinct advantages over muscle stimulation. First, fewer electrode implantations are required to evoke complex functions that involve synchronous activation of multiple muscle groups. For example, stimulation of the pudendal nerve in both animal models and SCI survivors has been shown to restore urologic function via contraction of the detrusor muscle in tandem with relaxation of the external urethral sphincter [65–67]. Second, peripheral nerve stimulation can simultaneously activate multiple muscles innervated by the stimulated nerve, allowing more robust responses from a single stimulation site [68]. Third, peripheral nerves contain both motor and sensory fibers [69]. As such, nerve cuff electrodes can be used for both stimulating motor fibers and for recording sensory information, thus providing an avenue for creating a feedback control of stimulation to optimize stimulation-evoked function.

Implantable peripheral electrical stimulation is not without problems. First, sustained muscle activation can be suboptimal

due to muscle fatigue associated with extracellular stimulation [70]. Second, existing implantable stimulator and battery technology limits the number of stimulation channels available. Third, these systems have limited ability to selectively activate specific nerve fascicles and/or axons, which can cause stimulation spillover, leading to the redundant activation of muscle groups or the co-activation of agonist and antagonist muscles.

Epidural Electrical Stimulation

In recent years, epidural spinal cord stimulation has emerged as a form of FES [37, 71–73]. Epidural stimulation relies on the application of electrical currents to the dorsal surface of the spinal cord. Studies in rodent models of incomplete SCI suggest that epidural stimulation enhances neural plasticity and, when combined with intense rehabilitation and pharmacological therapy, can lead to recovery of volitional movements [74, 75]. In humans, epidural stimulation of the spinal cord, combined with intense physical rehabilitation, was capable of promoting recovery of motor function in the lower limbs as well as improve bowel, bladder, and sexual function in a small group of patients ($n = 4$) with cervical and thoracic spinal cord injuries [71, 72]. Additionally, a recent clinical trial in individuals ($n = 9$) with cervical cord lesions (ranging from C3 to C6) found that epidural stimulation of the lower thoracic spinal cord evoked near maximal contraction of expiratory muscles. This, in turn, improved the expulsion of lung secretions, which can decrease the risk of pneumonia and thus reduce the morbidity and mortality rates associated with respiratory complications [37, 38, 76].

Despite this promising outlook, the mechanism by which epidural stimulation restores function following SCI is not well understood. Studies suggest that motor responses evoked by epidural stimulation are likely the result of indirect modulation of motor pathways via activation of spinal interneurons and afferent sensory fibers [74, 77, 78]. Unfortunately, non-selective activation of adjacent or contralateral spinal circuitry may result in undesired motor responses. For this reason, efforts are focused on understanding the mechanisms of action of epidural stimulation and optimization of stimulation configurations for restoration of motor function [79].

Intraspinal Microstimulation

Intraspinal microstimulation (ISMS) is an investigational form of FES in which electrodes are directly implanted into the spinal cord [80]. Its application was first explored in the 1970s by Jankowska and colleagues, who used ISMS to investigate the interneuronal connections involved in reciprocal inhibition of the reflex pathways of cats [81–83]. Since then, ISMS has been used extensively to characterize functional organization of spinal motor circuitry in frogs [84–88], rats [89], and cats [90, 91], and to restore fore limb function in the macaque monkey [92], and hind limb weight bearing and stepping following SCI in cats [93]. In addition, ISMS has been investigated, in both human [94–96] and animals models [97–100] as a means of restoring of bladder function [94, 96, 101, 102].

Interestingly, it has been suggested that nerve fiber activation using ISMS is in line with the natural physiologic order as opposed to the reverse order evoked by peripheral nerve stimulation [21]. If so, ISMS-evoked activation of low force, fatigue-resistant muscle fibers could enable standing, stepping, and posture control for durations that surpass those of conventional FES strategies.

Unfortunately, technological limitations have prevented clinical translation of ISMS. Specifically, existing ISMS techniques rely on repeated insertion and testing of stimulating electrodes without a priori knowledge of optimal stimulation targets. Each electrode penetration into the spinal cord can result in tissue damage, a critical factor in assessing ISMS efficacy [103–105]. Additionally, existing electrode implantation techniques rely on anatomical landmarks of the dorsal spine (i.e., spinous and transverse processes and facet joints) and spinal cord (i.e., dorsal fissure, bilateral posterior spinal arteries, and dorsal root entry zones), which are not reliable predictors of stimulation-evoked function [106].

NEUROPROSTHETIC FES SYSTEMS

Neuroprosthetic systems rely on one or more FES modalities to restore function lost to neurologic disease or injury (Fig. 16.3). These systems typically comprise an electrical pulse generator, a power source, lead wires, stimulating electrodes, and control algorithms.

Lower Extremity Systems

Several multi-channel stimulator systems that rely on intramuscular or peripheral nerve stimulation technology have been developed for restoring lower limb function. For example, the Praxis FES-22 system (Neopraxis Pty. Ltd., Lane Cove, Australia), derived from cochlear implant technology (Cochlear LTD, Sydney, Australia), has 18 implanted epineural electrodes. The Praxis system is unique in that it combines stimulation of lower limb muscles with stimulation of anterior sacral roots for bladder control. In a cohort of three SCI patients, the Praxis FES-22 was capable of achieving short-distance stepping and periods of standing of up to 60 minutes [107, 108]. However, attempts to utilize nerve root stimulation of the lumbosacral plexus for lower limb function and bladder control have lacked selectivity due to axonal reorganization within plexus structures [109, 110].

A “Stand Up And Walk” initiative from the European Union produced a 16-channel neuroprosthetic device that relies on nerve-cuff electrodes. This device was implanted in two paraplegic patients, who achieved short-term standing and assisted walking [31, 111]. Researchers at Case Western Reserve University and the Cleveland Veterans Affairs Medical Center have also developed a 16-channel stimulator for exercise, standing, and ambulation [18, 112, 113]. This system uses epimysial and intramuscular electrodes implanted into the quadriceps femoris and gluteus medius muscles, as well as lumbar erector spinae muscles, hip flexors, and ankle extensors [64]. The most widely used device has been the Parastep system (Sigmedics Inc., Fairborn, Ohio), which became commercially available in 1994. The Parastep system combines surface stimulation of the quadriceps muscle for knee extension with peripheral nerve stimulation for peroneal nerve flexion [114].

Although these systems are capable of restoring lower limb function, their clinical application has been limited by difficulties associated with optimal control of stimulation required to restore normal grasping patterns or stepping kinetics during locomotion. Additionally, rapid onset of muscle fatigue limits the user’s ability to perform functional tasks such as standing or stepping for extended periods of time.

Upper Extremity Systems

Similar to their lower extremity counterparts, multiple FES systems have been developed for restoring function to upper limbs following SCI. For example, the Bioness H200 (Bioness Inc., Valencia, CA), a commercially available stimulator, is capable of restoring basic hand grasp via transcutaneous stimulation of hand muscles [115, 116]. Similarly, the Bionic Glove, a three-channel transcutaneous stimulator system, is capable of evoking tenodesis grasp by controlling finger extension, flexion and thumb opposition [117]. While these neuroprostheses are non-invasive and generally inexpensive, they require cumbersome donning and doffing that increase the need for caregiver assistance. For this reason, implantable devices are better suited for chronic applications [63]. One such system is the Freehand system (Neurocontrol, Cleveland, OH), comprising an implantable stimulator connected to eight epimysial or intramuscular electrodes implanted in muscles of the hand and forearm. The implanted stimulator is both powered and controlled by a radio-frequency link to an external control unit [34, 63, 118]. While success has been achieved in restoring some gross motor upper extremity activities such as shoulder movement and hand grasp, control of fine motor function remains elusive due, in part, to the need for increased muscle selectivity and a corresponding number of stimulation channels.

Urologic Systems

Individuals living with SCI have described the restoration of urologic function as their top priority for improving quality of life [119, 120]. To that end, multiple implanted electrical stimulation modalities have been investigated for the restoration of urologic function and bladder control. Of these modalities, sacral nerve root stimulation has been the most widely applied [121]. It delivers epidural or intrathecal electrical stimulation to the sacral roots (S2-S4) to suppress bladder wall or detrusor muscle hyperactivity while increasing external urethral sphincter contractile strength, thereby increasing bladder volume and decreasing incontinence [120, 122]. A study of 42 patients with complete SCI, who

were implanted with sacral nerve root stimulation between 1987 and 2000, reported increased continence (54%), improved quality of social life (54%), and decreased urinary tract infection rates (68%) compared to conventional bladder management techniques [35].

Another modality for restoring bladder function is electrical stimulation of the pudendal nerve [67], which increases bladder capacity and continence by inhibiting the micturition reflex and abolishing contractions of the detrusor muscle [36]. By stimulating pudendal nerve afferents in ten SCI patients with detrusor hyperreflexia, Vodusek and colleagues reported an increase in micturition threshold in tandem with improvements in detrusor inhibition and urinary continence [123]. A study of 30 patients who had urinary voiding dysfunction with origins other than SCI compared stimulation of the S3 sacral nerve root to pudendal nerve stimulation [36]. In this study, 79% of patients reported pudendal nerve stimulation was more effective than sacral nerve stimulation for improving urinary retention, while 21% of patients found the reverse to be true. Overall, there was a 63% reduction of symptoms associated with voiding dysfunction in patients who received pudendal stimulation and only a 46% reduction in patients who received sacral nerve stimulation. Results from this study in non-SCI patients showed that pudendal nerve stimulation can improve urinary function via activation of neural circuitry that remains intact in SCI patients. Thus, this technique could be relevant for restoring function in patients with SCI as well.

Tibial nerve stimulation has also been shown to be a safe and effective treatment option for management of overactive bladder syndrome, a comorbidity observed in SCI subjects, via afferent modulation of the sacral nerve plexus [124]. A randomized, multi-center study comparing the effectiveness of percutaneous tibial nerve stimulation to extended-release of the pharmacologic agent tolterodine in 100 adults with increased urinary frequency showed that patient assessments of overactive bladder symptoms were significantly improved with tibial nerve stimulation [124]. These findings also have implications for treatment of individuals with SCI.

Respiratory Systems

Mechanical ventilation via chronic positive-pressure is necessary for SCI patients who cannot breathe on their own. Unfortunately, mechanical ventilation can lead to respiratory complications such as posterior lobe atelectasis, barotrauma, and pneumonia [125], which are the leading cause of death among ventilator-dependent SCI patients [125]. The diaphragm muscle is responsible for respiratory inspiration and accounts for approximately 65% of the lung's vital capacity [126, 127]. Respiratory FES systems can restore respiration following high-level SCI, thus eliminating the need for mechanical ventilation, by stimulating the diaphragm or the phrenic nerve, which enervates the diaphragm [126].

A prospective clinical study compared phrenic nerve pacing in a group of 64 mechanically ventilated patients who were divided equally among those who had intact phrenic nerves ($n = 32$) and those whose phrenic nerves were damaged ($n = 32$). The authors concluded that phrenic nerve pacing reduced upper airway infections and improved quality of speech and perceived quality of life [128].

Diaphragm pacing, a second form of FES-driven respiration that involves placing intramuscular electrodes into the diaphragm and intercostal muscles, has been shown to successfully eliminate the need for mechanical ventilation in some patients [129–131]. A study of ventilator-dependent SCI patients showed that 16 (73%) subjects were completely free of ventilator support approximately within 10 days following stimulator implantation; two (9%) were free of ventilator support in approximately 180 days; and three (14%) had partial weans, using diaphragm pacing during the day and mechanical ventilation at night [132]. One patient (4%) had life-prolonging interventions withdrawn [132].

LIMITATIONS OF EXISTING FUNCTIONAL ELECTRICAL STIMULATION SYSTEMS

Despite the functional capabilities of many FES systems, widespread usage by the SCI population has been hindered by technological limitations. The inability to selectively control

stimulation-evoked responses remains the principal barrier to the clinical application of FES systems. This limited selectivity can be attributed to the narrow number of available stimulation channels, which in turn hinders the ability to target specific muscles for fine motor control. Additionally, electrical spillover into adjacent excitable tissue can lead to undesirable activation of agonist and antagonist muscles.

Another barrier to clinical use is the large amounts of electrical energy required for multi-channel FES to evoke function via conventional stimulation technologies, which makes fully internalized power sources unfeasible. To accommodate these high power needs, commercially implantable stimulators are typically powered externally via transcutaneous radio-frequency links, which constrain system versatility (e.g., aquatic rehabilitation).

In addition, most FES systems rely on preset stimulation paradigms that are arranged in a queue and selected by the user. Most systems work in an open-loop configuration and do not receive input from feedback sensors, which is critical for optimizing stimulation and improve the evoked responses. As a result, most neuroprosthetic controllers are incapable of modulating stimulation in real-time in response to changing conditions in the system or the environment, nor do they account for motor response variability. Finally, muscle fatigue resulting from extracellular stimulation limits the duration of practical FES use. Thus, future technology should focus on adaptive control strategies that account for both the user's environment and optimized system performance to complete the desired motor tasks.

FUTURE DIRECTIONS

Before widespread application of FES technology can be achieved, numerous challenges must be overcome. The following are among the technological advances that should be considered in designing future FES systems and devices:

- wirelessly controlled, multi-channel stimulators with on-board, versatile control systems that integrate feedback signals [20, 100, 133] and are resistant to external interference

- control strategies that integrate user-generated motor commands that reflect intention generated by higher brain centers [134–136]
- high-efficiency implantable or rechargeable power sources in order to decrease power consumption and recharge time
- advanced stimulation paradigms, such as interleaved stimulation, to optimize muscle fiber recruitment and reduce muscle fatigue [63, 137–141]
- hybrid systems that combine multiple FES modalities and assistive orthoses so as to reduce physical strain, muscle fatigue, and FES energy consumption, while improving overall mechanical stability [142–144]
- novel biocompatible electrodes that: (1) allow increased selectivity of motor responses and reduce electrical spillover into adjacent non-targeted tissue; and (2) reflect the properties of the intended tissue environment to minimize tissue damage and reduce the body's natural reactions to foreign bodies.

CONCLUSIONS

Over the past few decades, significant advances in the field of FES have allowed restoration of various functions whose loss due to SCI was once considered irreversible. However, integration of FES systems into everyday life remains challenging. As research efforts focus on minimizing system footprint and on technological advances in stimulation and control strategies, next-generation devices will hopefully expand the clinical utility and long-term use of FES. In turn, this will help alleviate the physical and financial burden of SCI, and most importantly, will improve outcomes, functional recovery, and quality of life for those living with SCI.

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PART III

RESEARCH ON MECHANISMS OF DBS

AND NEUROMODULATION



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Chapter 17

Theories of Deep Brain Stimulation Mechanisms

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INTRODUCTION

This chapter reviews prominent hypotheses about the various neuronal, physiological, and metabolic mechanisms that underlie the therapeutic benefit of deep brain stimulation (DBS). DBS was first used to treat neurologically-based movement disorders, such as tremor associated with Parkinson's disease (PD), and is widely used for essential tremor and generalized dystonia as well as PD [1–3]. The application of DBS is rapidly expanding to other neurologic and psychiatric conditions, such as Tourette syndrome, epilepsy, depression, obsessive-compulsive disorder, and chronic pain [4–8]. However, because of its long history as an effective treatment for movement disorders, most hypotheses of mechanisms of DBS action are specific to those conditions and the effects of stimulating different nuclei within the basal ganglia-corticothalamic network.

The DBS procedure consists of implanting a multi-contact lead in a predetermined anatomical target with known therapeutic

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outcome. Targets vary with the specific disorder, the presence of co-morbidities, and with other neurological or psychiatric complications. In patients with PD who do not have psychiatric co-morbidities, the target is typically the *sensorimotor region of the subthalamic nucleus* (dorsal STN); for those with psychiatric co-morbidities, the target is usually the *internal segment of the globus pallidus* (GPi) [9, 10]. Recent studies of DBS for PD in humans and in non-human primate models of PD have also shown a therapeutic effect when targeting *pedunclopontine nucleus* (PPN) (mainly for posture control) [11] and the *external segment of the globus pallidus* (GPe) (mainly for tremor) [12, 13]. In generalized dystonia, the *posteroventral GPi* is typically targeted using bilateral DBS electrodes [14], although in some cases of dystonia, the STN is also a viable target [15, 16]. In secondary dystonia, the *posterior ventrolateral thalamic nucleus* has been targeted [17]. The principal target for essential tremor is the *ventral intermediate nucleus of the thalamus* (VIM) [18]. For those patients with essential tremor who are co-morbid with PD, the STN is the target of choice [19].

The central mechanism(s) of DBS involved in mediating therapeutic benefit continue to be debated, and given the multiple number of central anatomical sites targeted by DBS, it is highly unlikely that the mechanisms by which DBS achieves therapeutic success are comparable across targets and disease states [20]. However, certain general principles may hold. This review will focus only on early and contemporary hypotheses of the DBS mechanisms that attempt to explain its therapeutic effect on neurological movement disorders for which STN and GPi have been the principal anatomical targets.

HYPOTHESES OF DBS MECHANISMS

Evidence from a number of multidisciplinary sources has engendered several hypotheses about the mechanisms of DBS action [21–30]. As noted by Lee et al. [31, 32], four of these hypotheses have gained prominence and involve local changes in the stimulated brain nuclei and distal changes via activation and/or inhibition of efferent outputs to respective target nuclei within the basal ganglia-corticothalamic network, an interconnected network of nuclei that includes the STN, GPe,

GPe, *substantia nigra pars reticulata* (SNr), *substantia nigra pars compacta* (SNc), *caudate putamen* (striatum in rodents), VIM of the thalamus, and *cerebral cortex* (orbitofrontal, prefrontal, sensorimotor, supplementary motor, anterior cingulate, and insular cortices).

These hypotheses include (1) *depolarization block* (local lesion-like suppression of action potential generation in neuronal cells within the stimulated site and those that project out of it); (2) *synaptic depression* (loss of connectivity between the site of stimulation and its projection targets due to a depletion of neurotransmitters in the terminals of the targets of the stimulated site); (3) *synaptic modulation* (activation of local and distal neuronal terminals that inhibit and/or excite terminal afferent inputs and efferent outputs of the stimulated site); and (4) *network jamming* or *modulation* (a more global effect of DBS that involves nullification or resetting pathological anti-oscillatory activity in the basal ganglia-corticothalamic network). The evidence for each of these hypotheses is summarized below.

Depolarization Block

Prior to DBS, thalamotomy, an ablation surgery (i.e., excision or lesioning of brain tissue) in the thalamus, was the most common neurosurgical procedure for medically refractive tremor associated with PD [33, 34]. Because the effects were largely the same (albeit irreversible) as those in DBS, the earliest hypothesis of DBS mechanisms attempted to reconcile the similarity in clinical outcomes from thalamotomy and DBS by proposing that the high frequency stimulation (HFS) used in DBS inhibited neurons and decreased output from the stimulated site. The depolarization block hypothesis proposed that HFS applied at the same frequency and amplitude parameters that are typical of DBS inhibited local neurons and decreased output from the stimulated site [35, 36].

This notion gained support from a number of *in vitro* and *in vivo* animal studies. For example, electrolytic lesioning of the STN reversed the cardinal symptoms of PD in the parkinsonian (MPTP dopamine neurotoxin-depleted) non-human primate model [37]. In rat brain slices, Magarinos-Ascone et al. [38] showed that DBS-like HFS initially activated, but subsequently silenced cells

within the STN. This effect was not considered presynaptic depression, but rather a gradual inactivation of Na^+ -mediated action potentials—that is, a depolarization block. In further support of local cell inactivation, Beurrier et al. [39] used the patch-clamp electrophysiological recording technique in a rat brain slice and found that HFS of the STN blocked cellular activity post-stimulation, an effect considered similar to blockage of voltage sensitive Na^+ channels. In contrast to this proposed Na^+ inactivation mechanism, Shin et al. [40] demonstrated in the rat brain slice of the entopeduncular nucleus (the *analogue* of the primate GPi) that elevated extracellular K^+ depressed neuronal activity in a way that was comparable to that observed with HFS.

In studies in vivo using the parkinsonian (6-OHDA dopamine neurotoxin-depleted) rodent model, Benazzouz et al. [36] demonstrated that HFS of the STN decreased neuronal activity in the SNr and entopeduncular nucleus, and increased activity in the GPe and the ventral lateral nucleus of the thalamus, a result similar to that observed following electrolytic lesioning of the STN. In intact rats, Garcia et al. [41] found that STN HFS suppressed local neuronal spontaneous activity and spike generation. Moreover, systemic pretreatment with either excitatory metabotropic and ionotropic glutamate receptor or inhibitory gamma-amino butyric acid (GABA) antagonists could not alter or prevent this effect. These latter findings suggested that the effect was not mediated by synaptic receptors, but rather involved voltage-gated ion channels.

In patients with PD, electrophysiological recordings adjacent to a microstimulating electrode in the STN have shown that 100–300 Hz constant-current stimulation predominantly inhibited local cell activity (60 neurons/12 patients) [42]. Indeed, GPi stimulation using microstimulating electrodes has been shown to suppress neuronal firing activity in the parkinsonian (MPTP dopamine neurotoxin-depleted) non-human primate model [43] and in humans with PD (10 μA , 5 Hz, 150 μs pulses; 23 neurons/5 patients) [44]. In marked contrast, a more recent electrophysiological study of patients with PD by Carlson et al. [45] showed that neuronal firing rate was unchanged during and upon termination of STN DBS. A subset of cells displayed altered firing patterns with a predominant shift toward random firing. The distinct differences between the findings of Carlson

et al. [45] and those of Filali et al. [42] and Dostrovsky et al. [44] may be attributed to the fact that unlike the earlier studies, Carlson and co-workers used clinically relevant stimulation parameters (3–5 V, 80–200 Hz, 90 to 200 μ s pulses; 33 neurons/11 patients), delivered through a clinical DBS electrode (Medtronic 3389 human DBS 4-contact electrode), rather than a microstimulating electrode. These investigators concluded that rather than inactivating the STN, DBS provides a null signal via the STN to basal ganglia-corticothalamic circuitry that has been altered by PD.

However, several *in vitro* metabolic studies of STN cells during HFS lend additional support to the depolarization block hypothesis. For example, Salin et al. [46] found a reduction in cytochrome oxidase I (CoI) mRNA (a marker of neuronal metabolic activity) in STN cells during STN stimulation in the dopamine (6-OHDA) lesioned rodent. In addition, Tai et al. [47] found a reduction in cellular firing and neuronal metabolic activity (CoI mRNA) in STN and SNr cells of intact and SNc dopamine (6-OHDA) lesioned rodents. Overall, these relatively early findings suggest that the therapeutic action of STN and GPi DBS may reside on its capacity to suppress the action potential activity of neurons within DBS targeted brain nuclei.

Synaptic Depression

Unlike the depolarization block hypothesis, which holds that there is less output from a stimulated site due to inactivation of neuronal spike generation, the synaptic depression hypothesis and the synaptic modulation hypothesis (discussed in the next section) focus on neuronal synapses and propose that DBS affects neurotransmission. They differ in the mechanisms by which neurotransmission is disrupted. The synaptic depression hypothesis proposes that all local neurons activated by DBS are unable to maintain stimulus-locked high frequency neurotransmission on distal efferent targets and that the reason for this failure is the depletion of terminal vesicular stores of neurotransmitters, such as glutamate and GABA [48, 49].

Neurochemical studies of synaptic action during HFS provide some support for this hypothesis. For example, patch-clamp electrophysiological recordings from giant synapses in the mouse auditory brain stem suggest that the short-term synaptic

depression brought about by HFS (>100 Hz) can be largely attributed to rapid depletion of a readily releasable pool of vesicles. In addition, HFS of presynaptic terminals significantly enhances the rate of replenishment of the vesicular pool, and Ca^{2+} influx through voltage-gated Ca^{2+} ion channels is the key signal that dynamically regulates the refilling of the releasable vesicular pool in response to different patterns of inputs [48, 50]. However, HFS depletes the transmitter at a rate greater than the enhanced rate of vesicular replenishment.

Investigations of alpha-synuclein have added support to the concept of vesicle depletion resulting from HFS. Alpha-synuclein is a protein associated with docking vesicles at the presynaptic terminal membrane to enable release of neurotransmitters into the synapse. Mutations of alpha-synuclein have been implicated in the etiology and pathogenesis of PD, and Cabin et al. [51] found that alpha-synuclein knockout mice exhibit a selective deficiency of undocked vesicles without affecting docked vesicles. Electrophysiological recordings of CA1 synapses in hippocampal slices from these knockout mice demonstrated normal basal synaptic transmission, paired-pulse facilitation, and firing response to a brief train of HFS (100 Hz, 40 pulses). However, in response to a prolonged train of repetitive HFS, these mice exhibited a significant impairment in synaptic glutamate release that was capable of depleting glutamate from both docked and reserve pool vesicles. These findings suggest that the normal functioning of alpha-synuclein is required for regulating synaptic vesicle mobilization at nerve terminals, whereas mutations of alpha-synuclein may play a role in DBS-induced synaptic depression in PD.

In vitro electrophysiological studies are another source of support for this hypothesis. Studies have shown that HFS of subcortical white matter tracts projecting to motor cortex affects downstream postsynaptic responses in cortical neurons. Using whole cell recordings in the primary motor cortex (M1) and ventral thalamus of rat brain slices, Iremonger et al. [52] found that in response to HFS, M1 neurons exhibit an initial depolarization, after which the membrane potential returns to prestimulation levels. Neither GABAergic-mediated inhibition nor complete action potential failure in stimulated axons were associated with prolonged suppression of excitation during stimulation.

Instead, HFS caused a depression of excitatory synaptic currents in M1 postsynaptic neurons that appeared specific to the stimulated subcortical input. Overall, the data were consistent with the concept that axonal HFS produces a functional deafferentation of postsynaptic targets via depletion of presynaptic neurotransmitter.

Urbano et al. [53] also investigated the distal effects of HFS. Using voltage-sensitive dye imaging, they recorded field potentials during *in vitro* HFS of thalamocortical afferent axons from mouse brain slices to demonstrate a reduction in cortical activity with incremental increases in thalamic stimulation frequency. Optimal activation frequency was 40 Hz with a significant decrease in cortical activity at frequencies above 120 Hz. They concluded that this reduction represented neurotransmission failure as a consequence of transmitter depletion. Thus, under HFS-induced firing conditions, the compromised vesicular mechanisms in patients with PD may cause a consequent depletion of neurotransmitter vesicular stores in efferent terminals of the STN, and this may play a role in modulating neural activity during DBS in the basal ganglia-corticothalamic circuit.

Recently, Carron et al. [54] proposed that the two axonal routes (cell to terminal and terminal to cell) from a DBS-treated structure may have similar consequences, namely suppression of information flow to and from the stimulated structure. In the naturally occurring direction (cell to terminal), orthodromic spikes functionally de-couple the stimulated nucleus from the axon, excluding it from influencing its downstream target sites via depletion of terminal transmitter release. Thus, the pathological electrophysiological activity of glutamatergic STN output neurons no longer communicate with their target neurons.

In the opposite direction (terminal to cell), antidromic spikes prevent the nucleus from being influenced by monosynaptic (e.g., GPi, GPe, SNr, SNc) or polysynaptic (e.g., caudate putamen and cortex) afferent inputs, in essence antidromic collision [55]. As a result, the pathological synchronized activity arising from cortical and subcortical inputs can no longer propagate to the stimulated nucleus. The overall outcome has been described by Carron et al. [54] as a “reversible functional deafferentation” of the stimulated nucleus, cut off from its upstream and downstream nuclei to enable a new

resting state in the basal ganglia-corticothalamic circuit [54]. In this sense, one could consider the synaptic depression model of DBS to be an expansion and deeper explanation of the depolarization block hypothesis.

Synaptic Modulation

The synaptic modulation hypothesis holds that rather than depressing neuronal activity, DBS activates excitatory and/or inhibitory neuronal elements, including axonal fibers of passage that are in close proximity to the DBS electrode (see [56], for review). Excitation of inhibitory neurons would be expected to result in local synaptic inhibition via the release of inhibitory neurotransmitters such as GABA [57]. Excitation of excitatory neurons would be expected to result in local synaptic excitation via the release of excitatory neurotransmitters such as glutamate. Evidence for this hypothesis comes in part from electrophysiological extracellular recordings in patients with PD and in rodents and suggests that the nature of the excitatory/inhibitory effects of HFS may be site specific (i.e., GPi versus STN).

For example, electrophysiological recordings from GPi during HFS of the GPi have shown inhibition of local spontaneous activity lasting 10–25 ms [44]. Interestingly, the duration of the observed GPi activity corresponds to a typical GABAergic inhibitory post-synaptic potential (IPSP). These findings suggest that GPi HFS selectively activates GABAergic axon terminals synapsing in the GPi, likely arising from small spiny GABAergic neurons in the caudate that densely project to the GPi and, to a lesser degree, from the GPe GABAergic projections to the GPi [58]. These projections are thought to elicit GABA release to strongly inhibit GPi neurons [44].

The GPi also receives excitatory glutamatergic inputs from the STN [59], and thus, excitatory afferent terminal inputs from the STN are also activated by the stimulation. However, the predominance of GABAergic inputs to the GPi, likely overcomes this glutamatergic excitation [58]. These findings are consistent with the fact that patients with PD gain therapeutic benefit from microinfusions of the GABA agonist *muscimol* into either the VIM [60], which has relatively dense GABAergic innervation, or STN [61], a benefit that is comparable to DBS applied to the same regions.

In contrast to recordings from GPi, electrophysiological recordings from the STN in patients with PD revealed a general lack of change in firing rate, with a subset of cells showing altered firing patterns and a shift toward random firing during or after STN DBS [45]. Thus, a more precise description of the effects of DBS may be that it causes both local synaptic inhibition and excitation, depending on the site of stimulation. Support for this possibility comes from intracellular recordings in the rat STN showing that STN HFS activates both glutamatergic and GABAergic afferents and generates both local excitatory postsynaptic potentials (EPSPs) and IPSPs in STN neurons [62]. It has also been demonstrated that these postsynaptic potentials could be completely blocked by bath application of glutamate and GABA antagonists. In addition, because the inhibitory inputs are derived mainly from the GPe, and to a lesser extent the GPi [63], and the relatively denser excitatory inputs to the STN are known to originate from the cerebral cortex [64–67], it is conceivable that the EPSPs and IPSPs seen during STN HFS may result from stimulation of both descending cortical inputs to the STN, which generate glutamate-mediated EPSPs, and GPe inputs to STN, which generate GABA-mediated IPSPs. A recent study confirmed that inhibitory responses induced by GPi HFS were mediated by GABA_A and GABA_B receptors [68]. Together, these findings suggest that HFS, at least in the STN, activates predominately excitatory afferent axons in the STN, an effect that appears dependent on the weighted composition of the inhibitory and excitatory axon terminals in the STN, compared to the GPi.

Interestingly, a recent optogenetics study has shown that motor symptoms in parkinsonian rats can be markedly ameliorated via selective stimulation of cortico-STN afferent axons without activation of STN efferent axons [69]. This finding suggests that activation of cortico-STN afferent axons may exclusively account for the therapeutic benefits seen with STN DBS.

In addition to local synaptic inhibition and excitation, DBS may also activate local excitatory glutamatergic and/or aspartergic projection axons, causing distal synaptic excitation, including activation of fibers of passage. HFS activation of glutamate/aspartate-containing projections from the STN to GPi, GPe, and SNr would be expected to increase the release of these excitatory amino acids in these specific target nuclei [70, 71]. Indeed, Maurice

et al. [72] have shown that HFS of the STN in rats increases the activity of SNr cells, likely a result of monosynaptic activation of STN-SNr glutamatergic projections. This notion was supported by the fact that the recorded latency of the evoked excitation matched the conduction time of subthalamonigral neurons. In addition, Hashimoto et al. [73] found that in MPTP-lesioned non-human primates, STN HFS results in the development of a more regular pattern of firing activity that is concomitant with an increase in the mean discharge rate of GPe and GPi neurons with short-latency excitation. HFS of inhibitory GPi GABAergic axonal projections to the thalamus has also been found to inhibit thalamic target cells [74].

Metabolic studies of STN HFS are also consistent with these observations. In MPTP-lesioned non-human primates that received 10 days of STN HFS followed by evaluation of synaptic and metabolic activity, Meissner et al. [75] found an increase in 2-deoxyglucose (2-DG) uptake in the STN (a measure of increased neuronal activity) and a reversal of abnormally increased 2-DG accumulation in the GPi with a concurrent increase in neuronal metabolic activity (as measured by an upregulation in *Col* mRNA), suggesting global activation of GPi neurons. Thus, HFS may result in both distal synaptic inhibition and synaptic excitation by activating inhibitory projections to the GPi, presumably via STN glutamatergic projections to the SNr that, in turn, send GABAergic projections to the GPi.

Microdialysis studies in rats provide further support for the distal activation and inhibition effects of stimulating efferent target nuclei of the STN during STN DBS and show that changes appear to be related to stimulation frequency. For example, Bruet et al. [76] found that in both intact and dopamine-lesioned rats, unilateral STN HFS evoked a significant bilateral increase in striatal glutamate and GABA release. And Windels et al. [77] found that STN HFS caused a significant increase in extracellular glutamate concentration in the ipsilateral entopeduncular nucleus and SNr, while GABA was augmented only in the SNr. Their findings showed that extracellular concentrations were dependent upon the frequency levels of stimulation. Basal extracellular concentrations of GABA remained the same in the entopeduncular nucleus, regardless of the applied frequencies. In contrast, GABA levels in the SNr increased only when stimulation increased from

60 to 350 Hz. They also found that maximal extracellular glutamate concentrations in the entopeduncular nucleus and SNr were achieved at 130 Hz and showed no change with up to 350 Hz stimulation. Thus, STN HFS produces frequency-dependent release of excitatory and inhibitory neurotransmitters in the various efferent target nuclei of the STN.

These results supporting distal activation, referred to as the “distal synaptic modulation hypothesis,” have been explored in computational models of both GPi and STN. For example, computational simulations of HFS stimulation by McIntyre et al. [78] and Johnson and McIntyre [20] showed that in the GPi, subthreshold HFS suppresses intrinsic firings in cell bodies, while suprathreshold HFS generates efferent outputs in concert with the stimulation frequency in the projection axon, independent of the soma. This decoupling of responses between the axon and soma may explain why *in vivo* extracellular recordings report both inhibition of the soma and excitation of efferent targets during DBS. However, as noted earlier, it may also be that GPi HFS fails to activate cell bodies of GPi neurons due to strong GABAergic inhibition. Regardless, these computer simulations still suggest that GPi HFS may excite efferent axons and provide inhibitory input activity to the thalamus at the same rate as the stimulus frequency. Most significant, other computer simulations found that this separation or decoupling of axonal and somatic activity was associated with STN stimulation. Overall, converging electrophysiological evidence and computational models point to a combination of DBS effects which include both local and distal inhibitory and excitatory synaptic modulation.

Studies of HFS-generated dopamine release in the STN help support the concept of local, distal, and mixed synaptic modulation effects. Specifically, HFS of the dorsal STN may result in dopamine release from surviving dopaminergic neurons projecting to the caudate putamen and therefore may contribute to the therapeutic effect of DBS when it is supplemented with low doses of L-DOPA. The axons of SNc dopaminergic neurons lie immediately dorsal to the STN, provide collateral inputs to the STN, and are sometimes purposely targeted to attain maximum stimulation efficacy [79, 80]. In addition, glutamatergic terminals arising from the STN make synaptic contact with dopaminergic dendrites within the SNr [81]. These anatomic relationships suggest that dopaminergic

nigrostriatal activity may be increased by STN HFS. In this regard, Lee et al. [82] recently reported that STN HFS evokes glutamate release locally in the STN. Thus, STN HFS-evoked glutamate release in the SNc may increase firing of dopaminergic neurons, which, in turn, enhance dopamine release in the caudate putamen.

In addition, using *in vivo* electrochemical recording techniques, investigators have shown that HFS of either the STN or dopamine axons in the closely adjacent nigrostriatal dopaminergic pathway evoked striatal dopamine release in rats [83], pigs [84], and non-human primates [85]. Consistent with these findings, several *in vivo* microdialysis studies have shown that STN HFS in normal and dopamine-lesioned rats increases extracellular levels of dopamine metabolites dihydroxyphenylacetic acid and homovanillic acid [86–88], indicators of enhanced dopamine release. STN HFS-evoked increases in extracellular concentrations of striatal dopamine could not be detected without first administering the dopamine reuptake inhibitor, nomifensine, and stimulating for prolonged durations (20 min) [89]. In contrast, Bruet et al. [90] have shown that HFS STN can induce a significant increase of extracellular DA in the striatum in normal and dopamine-lesioned rats in the absence of dopamine reuptake inhibition.

The discrepancies between these microdialysis studies may be due to methodological differences and, in particular to the anesthesia employed. Meissner et al. used the general anesthetic chloral hydrate, whereas Bruet et al. employed the gas anesthetic halothane in their studies. In rats, it has been shown that stable baseline levels of dopamine metabolites are maintained under halothane anesthesia, while the extracellular levels of dopamine metabolites gradually decline under chloral hydrate anesthesia indicating attenuation in basal dopamine neurotransmission [91]. Thus, to be able to measure HFS STN-evoked dopamine release, an anesthetic-dampened dopaminergic system compounded by a lesion may have necessitated the inhibition of dopamine reuptake by nomifensine [89].

Several positron emission tomography (PET) studies using [(11)C] raclopride binding to measure dopamine release have also failed to demonstrate significant raclopride displacement [92–95]. Raclopride is a competitive postsynaptic dopamine receptor antagonist. The rationale behind measuring radioactively labeled raclopride binding by PET is that dopamine release will

compete with and displace raclopride from its postsynaptic dopamine receptor binding site. Thus, increases in dopamine transmission (presynaptic release) will appear as a decrease in raclopride binding by PET. Overall, these *in vivo* PET findings in patients with PD suggest that STN DBS may not mediate its therapeutic effects via increases in striatal dopamine release. It is important to note however, that PET scanning with $[(11)\text{C}]$ raclopride has relatively poor temporal resolution and additionally requires a decrease in the PET baseline signal (raclopride displacement) of greater than 90% in order to detect a change in dopamine release [93, 96]. As well, adaptive changes in dopamine D2 receptor populations, such as receptor internalization and recycling, which occur with long-term STN DBS, may interfere with PET quantification of dopamine release in patients with PD [97]. Future studies using electrochemical or microdialysis recording of dopamine release during DBS surgery may resolve whether stimulation of axons of passage in the region of the dorsal STN or stimulation of neurons within the STN or both leads to enhanced dopamine release in the caudate putamen.

Network Jamming or Modulation

The neural jamming or modulation hypothesis proposes that DBS regulates and corrects pathological activity in the basal ganglia-corticothalamic network by interfering or “jamming” pathologic neuronal responses. This hypothesis is dependent upon the accuracy of several of the hypotheses discussed above relative to whether or not DBS causes mixed modulation (excitation and inhibition) or predominantly the suppression of efferents in the stimulated nuclei and their targets within the basal ganglia-corticothalamic network. It is the overall response of the basal ganglia-corticothalamic circuit to these messages or lack thereof that is most important. Critical neurophysiological studies on normal and pathological states in the basal ganglia-corticothalamic network have shown that movement disorders like PD result in specific changes in cellular activity. Computer simulations have modeled the effects of various stimulation frequencies and the regularity of neuronal activity on information transfer between synaptically connected neurons in the network. These computer simulations suggest that HFS results in an informational lesion

(neural jamming) either by altering the pathological signal so that it generates a normal firing pattern or by desynchronizing abnormal oscillations ([22, 98]; see [54], for review).

A detailed knowledge of ionic neuronal conductance and normal firing activity patterns within the basal ganglia-corticothalamic network is required to fully understand the principles of neural jamming. For purposes of this review, it is important to understand that the intrinsic membrane properties that generate rhythmic oscillations (from 10 to 40 Hz) in both STN and the thalamus enable neurons to discharge in both tonic and burst modes [99–101]. These membrane properties result from several different ionic conductances that include a channel hyperpolarizing-activated current (I_h) and a depolarizing potassium-activated calcium current (I_{CaK}) and sodium current (I_{NaP}) [102, 103]. As a result, depending on the input, STN neurons have two preferential frequencies: slow rhythmic firing at rest and high frequency firing. However, other investigators have shown that STN neurons can exhibit multiple neuronal firing patterns that are predominantly irregular (55–65%), but also can be in tonic (15–25%) and in burst modes (15–50%) [104]. In patients with PD, large amplitude irregular spike patterns or periodic spiking behavior have been recorded in the STN which have led to the following classification: (1) tremor cells (2–6 Hz); (2) cells with high (>10 Hz) frequency periodic activity; and (3) a combination of each [105]. Interestingly, in patients with PD who have limb tremor, many STN neurons display high frequency oscillations with a high degree of in-phase synchrony. Together, these results suggest that high frequency synchronized oscillatory activity is associated with the pathology that gives rise to tremor in PD patients.

Local field potential recordings in the human STN have shown an oscillatory activity in the beta frequency range (15–30 Hz), which is dramatically increased in PD ([106–109]; see, however, [110]). Although the exact relationship between oscillatory activity and PD symptoms remains to be determined, a study using dopamine-lesioned non-human primates suggests that STN HFS might at least partially exert its beneficial effects through the reduction of oscillatory activity in the STN network and consequently in

the entire basal ganglia-corticothalamic network [111], lending support to the “neural network jamming” hypothesis of DBS. Indeed, when STN DBS is added to computer models, a progressive reduction in STN power at both tremor and beta frequencies has been observed as the DBS frequency is increased, with resonance effects occurring for low frequency DBS (40 Hz). These findings are in agreement with experimental observations [98].

The neural network mechanisms that may be responsible for these basal ganglia-thalamic oscillatory activities are beginning to be revealed. For example, STN neurons have been shown to be part of a neural network involving interconnections with the GPi and GPe [57, 112] which generate synchronized oscillations [113, 114]. In these circuits, the GPe releases GABA onto STN neurons eliciting IPSPs with a subsequent rebound Ca^{2+} spike via activation of a low threshold calcium channel. This permits high frequency action potential generation in STN neurons that, in turn, via STN afferents, releases glutamate onto GPi/e neurons. Glutamate activation of GPi/e neurons thus provides for the next cycle of oscillation within the STN and GPi/e network. It has been posited that tremor generation in PD patients may result from these oscillations. As such, the disruption of these oscillations may be an important mechanism whereby STN DBS diminishes tremor. Indeed, recent studies have suggested that in addition to reciprocal STN-GP connectivity, cortical glutamatergic inputs to the STN and reciprocal GPe-STN interconnections are both important for the generation and amplification of the oscillatory activity of GPe and STN neurons in the parkinsonian state. These investigators have shown that the oscillatory activity in the STN is subsequently transmitted to the GPi which may contribute to manifestation of parkinsonian symptoms [115, 116].

SUMMARY

The four hypotheses reviewed in this chapter are clearly interconnected but also highly dependent on the site of stimulation and disease state. Given these circumstances, it is unlikely that a unifying “common” theory of the exact mechanism(s) of DBS action will ever be realized or, for that matter, necessary. As we

learn more about the anatomical, physiological, and metabolic similarities and differences between these disparate sites targeted by DBS for the same and different neurological diseases, a full understanding of their interconnectivity and interaction within the basal ganglia-corticothalamic complex will help identify which factors play a major or minor role in eliciting the best therapeutic benefit and which factors can be considered mere epiphenomena. It is important to note that non-neuronal glial cells, which constitute over 50% of cells in the brain, likely also contribute to the therapeutic effects of DBS via stimulation-induced release of glutamate and adenosine triphosphate (ATP) from astrocytes [117, 118] (see Chapter 18). Uncovering the neurophysiological, neurochemical, and metabolic mechanisms of DBS, including the anatomic connections that mediate the normalization of activity within the basal ganglia-corticothalamic network will allow for future development of improved and more effective DBS.

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Chapter 18

The Role of Astrocytes in Deep Brain Stimulation

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INTRODUCTION

The therapeutic success of deep brain stimulation (DBS) for movement disorders has led to its consideration for a rapidly expanding set of neurologic and psychiatric conditions—from obsessive compulsive disorder to depression and memory loss. This pressure to expand DBS applications makes it critical that *all* potential underlying molecular and physiologic processes that bear on its therapeutic action be investigated.

To date, research has understandably focused on neuronal changes. As mentioned in the previous chapter, DBS was initially thought to silence pathologically hyperactive neurons [1–3]. Technical advances then generated the theory that DBS directly inhibits neuronal elements close to the stimulation site and elicits axonal activation and neurotransmitter release [4–11]. Mathematical models suggested that because of the dissimilar

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excitability of neural elements, both soma inhibition and axonal activation can be expected at the DBS electrode site [6, 12]. None of these theories, however, address the role of astrocytes, which are more numerous than neurons and are known to make important contributions to neurotransmission, chemical homeostasis, synaptic plasticity, and control of blood flow [10, 13–16].

Forming a tripartite synapse with neuronal synapses, astrocytes are active players in neural signaling [17, 18]. In addition, they respond to high-frequency stimulation (HFS) by altering important regulators of neuronal network activity and inducing release of glutamate, ATP, and adenosine [10, 14–16, 19]. Astrocytes can modify extracellular neurotransmitter concentrations, which in turn decrease pathologic neuronal oscillations [16]. While the physiological actions of astrocytes in general, and in response to HFS in particular, have been extensively investigated, little attention has been paid to their impact on therapeutic DBS. This chapter focuses on the potential role of astrocytes in DBS therapy.

LOCAL EFFECTS OF HIGH-FREQUENCY STIMULATION ON GLIA

It is well documented that HFS triggers propagating astrocytic Ca^{2+} waves [20–22]. Initial studies showed that electrical stimulation evokes long-distance Ca^{2+} signaling [23] and that electrical stimulation of brain tissue activates glial cells and causes increases in calcium concentration within glial cytoplasm [24]. It is also well established that local activation of glial cells can lead to a wave of activation that propagates through the glial cell syncytium in the brain for distances as great as several centimeters [24, 25]. Increases in glial calcium, in turn, evoke the release of gliotransmitters, including ATP/adenosine, glutamate, D-serine, and PGE_2 [26, 27]. Release of these gliotransmitters can result in excitation or inhibition of neurons as well as the modulation of synaptic transmission and synaptic plasticity [28–31].

Astrocytic Ca^{2+} Signaling

Astrocytes express numerous neurotransmitter receptors and respond to neuronal activity by increases in cytosolic Ca^{2+} [32].

The ability of astrocytes to sense neuronal activity and respond with increases in cytosolic Ca^{2+} has been a topic of intense research [27, 33, 34]. Propagating Ca^{2+} waves can be stimulated by focal electrical stimulation, mechanical stimulation, lowering extracellular Ca^{2+} levels, or by local application of agonists [20, 26, 35–38]. High-frequency neuronal spiking has been shown to induce astrocytic Ca^{2+} waves in organotypic brain slices [39]. Generally, Ca^{2+} waves propagate at a velocity of $\sim 20 \mu\text{m}/\text{sec}$ and expand over a radius of ~ 50 to $300 \mu\text{m}$, which includes between 20 and 60 astrocytes per wave. Also, Ca^{2+} waves require activation of phospholipase C, with subsequent events leading to IP_3 production and release of calcium from IP_3 sensitive internal stores [40, 41].

Initially, it was proposed that propagation of Ca^{2+} waves was conducted by the diffusion of IP_3 and/or Ca^{2+} through gap junctions [35]. However, the role of gap junctions in calcium wave propagation was questioned in a study demonstrating that physically isolated astrocytes engage in Ca^{2+} waves. This finding suggests that an extracellular element mediates calcium signaling.

Using pharmacological approaches, it was later demonstrated that ATP was the diffusible messenger. The existence of several pathways for ATP release has been proposed, including Connexin (Cx)-hemichannels, P2X_7 receptors, or vesicular release [33]. Wave propagation is mediated by P2Y receptors, and it is likely that multiple purinergic receptor subtypes, including P2Y_1 , P2Y_2 , and P2Y_4 are involved [42]. Using bioluminescence imaging, it was shown that astrocytes can release ATP, which diffuses to surrounding cells resulting in increases in cytosolic Ca^{2+} concentration by activation of purinergic receptors [43–45]. Astrocytic Ca^{2+} waves thereby function as a local amplification mechanism: when an astrocyte reaches a certain level of activation, it releases ATP, which increases Ca^{2+} in neighboring cells and results in a local expansion of astrocytic activity [41, 46].

DBS-Evoked Astrocytic Glutamate Release

Another important gliotransmitter implicated in DBS action is glutamate [16]. Efficient excitatory signaling in the nervous system requires that levels of synaptic glutamate are exquisitely controlled, and astrocytes are thought to function in both glutamate uptake and release. Astrocytes have been shown to clear synaptic glutamate via specific sodium-dependent glutamate

transporters [47]. Most importantly, astrocytes respond to neuronal activity by exhibiting calcium waves [26, 48], which has been shown to lead to further glutamate release [49, 50]. In addition, several studies have now established that astrocytes contain vesicular glutamate stores that can be triggered to undergo exocytosis by: (1) mechanical stimulation [51]; (2) activation of ionotropic glutamate receptors [52]; or (3) activation of metabotropic glutamate receptors [53]. Previous studies have also demonstrated that HFS of hippocampal slices or astrocyte cultures can elicit astrocytic calcium waves [39, 54]. In addition to a vesicular mechanism, astrocytes also release glutamate through volume sensitive channels after ATP stimulation [55]. This implies that specific stimuli may recruit different gliotransmitter release mechanisms that may modify the spatio-temporal characteristics of subsequent neuronal responses.

A study by Tawfik et al. [16] found that DBS of the ferret brain slice *in vitro* resulted in both glutamate and adenosine release. The glutamate release was still evoked in the presence of the Na^+ channel blocker tetrodotoxin (TTX), but was eliminated with the vesicular H^+ -ATPase inhibitor, bafilomycin, and the calcium chelator, BAPTA-AM. Further, electrical stimulation of purified primary astrocytic cultures was able to evoke intracellular calcium transients and glutamate release, and bath application of BAPTA-AM inhibited glutamate release in this setting. These results suggest that vesicular astrocytic neurotransmitter release may be an important mechanism by which DBS is able to achieve clinical benefit. The prime location of astrocytes at the tripartite synapse allows them to synchronize neuronal responses, an effect which has been linked to activation of extrasynaptic NMDA receptors [56]. Taken together, DBS-evoked glutamate release from astrocytes may modulate synaptic transmission in a variety of ways that are likely dependent on the nature and intensity of the inducing stimulus as well as CNS location.

HIGH-FREQUENCY STIMULATION AND ASTROCYTIC ATP RELEASE

ATP released during HFS has been visualized using a bioluminescence technique [57]. Thalamic slices (P18-21) were

perfused with a solution containing a mixture of luciferase and D-luciferin. Photons emitted when ATP catalyzes the oxidation of D-luciferin were imaged by a liquid nitrogen cooled CCD camera [41]. HFS triggered an abrupt increase in extracellular ATP around the stimulation electrode, which was sensitive to the polarity of stimulation. The negative pole (cathode) gave rise to a 5- to 10-fold higher ATP release than when the polarity was changed and the same electrode delivered positive stimulation (anode). This observation is of potential significance for DBS because clinical work has shown that only cathodic stimuli suppress tremor activity [58–60]. ATP release at the cathode was a direct function of the current amplitude and the frequency of stimulation. In addition, removal of extracellular Ca^{2+} from the bath solution to prevent synaptic release resulted in enhanced ATP bioluminescence, indicating that ATP release was primarily non-synaptic and likely resulted from efflux of cytosolic ATP. Thus, HFS triggers primarily non-synaptic release of ATP affecting widespread areas surrounding the stimulation electrode [61].

DBS-Evoked Astrocytic Adenosine

The modern era has seen the rise of rapid sampling electrochemical techniques, such as amperometry coupled to enzyme-linked biosensors and fast-scan cyclic voltammetry (FSCV) coupled to a carbon-fiber microelectrode (CFM), which enable mechanistic studies of DBS on sub-second time scales and in micron-sized space domains [62]. HFS-evoked adenosine release has been monitored in several studies with an adenosine biosensor (Sarissa Biomedical Ltd), and it was found that like ATP, adenosine levels increased as a function of both the frequency and current amplitude of HFS [63]. Removal of extracellular Ca^{2+} significantly increased adenosine release. Conversely, slices exposed to the ecto-ATPase inhibitor ARL-67156 (6-N,N-diethyl-D-beta, gamma-dibromomethylene ATP; 50 μM) exhibited a reduction in the HFS-induced adenosine increase ($41 \pm 5\%$ of vehicle treated controls, $p < 0.05$, t -test), suggesting that the primary source of adenosine originated from extracellular hydrolysis of ATP. ARL did not completely block the rise in adenosine, suggesting that ARL does not inhibit all extracellular ATP degradative enzymes [64, 65] or that adenosine was released by alternative pathways [65]. Thus,

HFS was consistently associated with prolonged increases in extracellular ATP and adenosine with stimulation frequencies greater than 100 Hz being most efficient. Of note, the clinical beneficial effects of DBS are markedly frequency-dependent and occur primarily, if not exclusively, at high frequencies over 100 Hz [66].

HFS-evoked adenosine release has also been measured using FSCV [15, 67]. FSCV generates a voltammogram, which is a plot of measured current versus applied potential that serves as a chemical signature to identify analytes. For example, the voltammogram of adenosine on the first scan reveals a single peak at +1.5 V corresponding to the first oxidation peak potential of adenosine. On subsequent scans a second oxidative peak appears at +1.0 V corresponding to oxidation of the first product of adenosine oxidation. These findings are consistent with adenosine undergoing a series of 2-electron oxidations as described by Swamy and Venton [68] utilizing FSCV procedures with T-650 CFMs *in vitro*. These peaks are clearly observed when voltammograms are plotted sequentially, with current intensity designated by pseudo-color.

Given that DBS results in robust release of ATP and subsequent adenosine-mediated inhibition of excitatory post-synaptic currents (EPSCs), it follows that administration of adenosine or adenosine agonists into thalamic nuclei should also be effective in reducing tremor. To test the anti-tremor effect of direct delivery of adenosine or the A1 receptor agonist, CCPA (2-chloro-N6-cyclopentyladenosine), Beker and colleagues inserted microdialysis probes bilaterally in thalamus of harmaline-induced tremor model in mice. Both adenosine (1–10 mM) and CCPA (10–50 μ M) reduced tremor with a potency comparable to DBS in the mice, indicating that activation of A1 receptors mediates the anti-tremor effect in the thalamus [14].

Adenosine Controls Network Activity

Adenosine is a potent neurotransmitter with pervasive and generally inhibitory effects on neuronal activity [69]. Pape [70] has shown in guinea-pig thalamic slices that adenosine hyperpolarizes thalamic relay neurons. This effect was thought to be due to an increase in membrane potassium conductance, inhibiting single

spike firing and promoting calcium-mediated burst discharges, and was non-additive to K^+ currents generated by near maximal stimulation of $GABA_B$ receptors. Interestingly, blockage of membrane K^+ conductance by barium unmasked a second response to adenosine: an outward shift of the current versus voltage relationship negative to -65 mV due to a decrease in amplitude and the rate of rise of the hyperpolarization-activated cation current, I_h . Both responses to adenosine were mimicked by selective A1 receptor agonists and reversibly blocked by the selective A1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX). The decrease in I_h by adenosine appeared to be mediated by inhibition of adenylyl cyclase activity and hence a decrease in the intracellular level of cyclic AMP, since local application of the adenylyl cyclase inhibitor 2',3'-dideoxyadenosine imitated the decrease in I_h [70]. In a resting state, low levels of extracellular adenosine tonically dampened neural activity, whereas the A1 receptor antagonist, DPCPX, increased spontaneous cortical activity. Conversely, adenosine or the A1 specific agonist CCPA potently suppressed local activity [69, 71]. Importantly, the release of ATP/adenosine during DBS appears to improve therapeutic DBS efficacy by reducing the adverse effects of DBS [14].

To analyze the role of adenosine in HFS, Bekar et al. [14] studied the effect of perfusion with an artificial CSF containing 1–100 μ M adenosine in thalamic slices. Adenosine suppressed the amplitude of excitatory postsynaptic potential (EPSP) with a maximal reduction of $76.13 \pm 6.47\%$ of control values and an ED_{50} of 3.35 ± 0.75 μ M. The inhibitory effect of adenosine was mediated by A1 receptors, since DPCPX (100 nM) reversibly attenuated the reduction. CCPA (1.0 μ M), a selective adenosine A1 receptor agonist, mimicked the action of adenosine by potently depressing EPSPs by $75.59 \pm 4.98\%$. Consistent with direct measurements of adenosine, the ecto-ATPase inhibitor ARL-67156 (6-N,N-diethyl-D-beta, gamma-dibromomethylene ATP; 50 μ M) reduced HFS-induced depression of EPSPs [72], suggesting that the accumulation of extracellular adenosine during HFS originated primarily from hydrolysis of ATP. A similar effect was observed in slices exposed to FFA (flufenamic acid; 50 μ M), which reduces ATP release by blocking connexin hemichannel opening [73]. In contrast, the NMDA receptor antagonist, APV (50 μ M) had no significant effect upon HFS-induced reduction

of EPSPs. Strikingly, HFS triggered a $101.75 \pm 13.13\%$ increase in EPSPs in slices prepared from mice with deletion of adenosine A1 receptors [74], whereas a reduction of EPSPs of $32.91 \pm 7.43\%$ was evident in littermate controls (A1R+/+). Combined, the analysis of thalamic slices provides direct evidence for a key role of adenosine A1 receptors in the depression of synaptic transmission during and after HFS, but also confirmed that axonal or synaptic mechanisms contributed to depression of directly stimulated pathways.

These findings also suggest that DBS may evoke the release of multiple neurotransmitter systems from astrocytes, including glutamate and adenosine. Determining which of these gliotransmitters is primarily responsible for the effects of DBS in human patients requires further investigation. However, these studies provide strong evidence for a role of gliotransmitter release in the modulation of neuronal responses important to the cessation of abnormal hyperactivity by DBS.

DISTAL EFFECTS OF HIGH-FREQUENCY STIMULATION ON GLIA

DBS may also have distal effects on the stimulated release of adenosine. Adenosine release can be measured in the striatum with chemical microsensors during electrical stimulation in the vicinity of the nigrostriatal dopaminergic tract [75]. Importantly, increases in extracellular adenosine appear to match elevations in cerebral blood flow caused by increased neural activity [76, 77]. Indeed, we have recently demonstrated that STN DBS elicits adenosine release in the striatum as measured by chemical microsensors (unpublished observation). Combined with brain imaging evidence that neural activity in the striatum is increased during DBS, the available data also suggest that striatal release of dopamine and adenosine are putative chemical mediators of STN DBS. However, a causal relationship between functional activation of the striatum and adenosine release in the same brain region has not been established. A major hurdle for establishing the functional anatomical effects of DBS and identifying the critical neurotransmitters involved in it is that simultaneous brain

imaging and monitoring of chemical-specific neurotransmitter release has not been conducted. To date, we are unaware of any studies that have combined these measurement modalities for the study of DBS mechanisms. However, fMRI studies in humans implanted with DBS systems are now beginning to be undertaken.

For example, to determine the pattern of functional magnetic resonance imaging (fMRI) activation at 3T MRI induced by STN DBS for Parkinson disease, Philips et al. [78] implanted five patients with percutaneously extended bilateral DBS electrodes placed in the STN. The authors reported that blood-oxygenation level dependent (BOLD) signal activation was seen in the ipsilateral basal ganglia in all five subjects and ipsilateral thalamus in six of the nine electrodes tested. Two of the electrode stimulations produced additional activation in the STN and/or substantia nigra region adjacent to the electrode tip. The authors concluded that therapeutically effective DBS of STN can be performed safely during fMRI at 3T and produces a consistent pattern of ipsilateral activation of deep brain motor structures.

Given that cerebral microvessels are extensively ensheathed by astrocytic processes [79], thereby physically linking the intraparenchymal vasculature with synapses, it is tempting to speculate that astrocytes are involved in the activity-induced hyperemia (i.e., excess blood in the vessels) [80, 81] that is seen in BOLD fMRI activation. In a study based on 2-photon imaging of cortex in adult mice, it was shown that photolysis of caged Ca^{2+} in astrocytic endfeet invariably triggered vasodilation [13]. Vasodilation averaged 18% corresponding to an almost 40% increase in local perfusion. A specific COX-1 inhibitor NS-398, as well as indomethacin, attenuated astrocyte-induced vasodilation. Furthermore, COX-1 immunoreactivity was strongly expressed around penetrating cortical arteries, suggesting that COX-1 vasoactive products mediated vasodilation [13]. More recently, O_2 tension has been shown to be a key determinant in release of agents mediating vasodilation versus vasoconstriction [82]. Taken together, these results suggest the intriguing hypothesis that in addition to local activation, astrocytes may also be activated at sites distal to DBS targets, depending on the neural networks affected by DBS.

DBS-ASTROCYTE MECHANISMS AND EFFECTS: A HYPOTHESIS

The cascade of events described in this section may be considered in generating a hypothesis of the effects of astrocytes on DBS. DBS results in immediate activation of neuronal soma and axons in a Na^+ channel-dependent manner and therefore, is TTX-sensitive. The firing of neuronal populations then results in release of neuronal neurotransmitters at both local and distal sites with network effects on post-synaptic neurons and astrocytes. In addition, DBS activates Ca^{2+} waves in astrocytes that are TTX-insensitive. The activated astrocytes release gliotransmitters, including glutamate and ATP, which may further propagate the Ca^{2+} wave locally and distally. The extracellular ATP undergoes a series of reactions by ectonucleotidases to produce adenosine with a rapid time constant of ~ 200 ms [83]. Through activation of A1 receptors, adenosine has a further effect on neuronal elements by membrane potential hyperpolarization through the opening of K^+ channels, as well as anti-oscillatory effects through a negative shift in voltage dependent activation of I_h . The primary effect of the local glutamate release is to cause membrane depolarization through glutamate ionotropic receptor activation and a positive shift in voltage dependent activation of I_h .

CONCLUSION

As noted in this chapter, we and others [7, 9, 15, 16, 84–86] have proposed that characterization of the understudied effects of glia on mechanisms of DBS on neurotransmission will provide a deeper understanding of its therapeutic benefit. Ultimately, this basic cellular and molecular knowledge will be critical to the development of advances in DBS technology that seek to improve surgical procedures and patient outcomes.

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Chapter 19

Electrochemical Measurement of Neurochemical Concentrations

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INTRODUCTION

Monitoring neurochemical and electrical changes is an important means of analyzing changes in brain neuronal activity evoked by high-frequency stimulation (HFS). Neurochemical changes include alterations in synaptic neurotransmitter release and possibly the release of adenosine from astrocytes. The standard experimental set-up for this type of analysis involves a hard-wired connection between the subject and an external monitoring device and computer, powered by line current. The wired connection between these devices and the subject makes it difficult to study brain function in awake, freely behaving animals [1, 2]. This fact as well as safety concerns has imposed limits on the potential for this type of research in human subjects.

Deep Brain Stimulation: Indications and Applications

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HFS varies according to the frequency (measured in hertz) and the intensity (measured in volts or current) of the stimulation. Changes in these parameters have neurochemical consequences, and hence consequences for behavior. At present, in the clinical setting of deep brain stimulation (DBS), parameter adjustments are conducted on a trial-and-error basis by a clinician-programmer using patient feedback and observable or experienced symptom changes, such as reduction in tremor associated with Parkinson's disease [3, 4]. However, not all behavioral changes are as readily observed. For example, major depression, obsessive-compulsive disorder, and other symptoms of neurologic or psychiatric conditions take time to abate following DBS and are less easily measured and quantified.

What is needed in both the experimental and the clinical settings is a versatile wirelessly programmable system, capable of adjusting stimulation and recording parameters in real time and of sustaining responses in dynamic environments. Such closed-loop devices should be designed to adjust stimulation parameters relative to stimulation-evoked changes in neural electrophysiologic and neurochemical activity.

The Mayo Clinic Neural Engineering Laboratory and the Division of Engineering have successfully developed a wireless instantaneous neurotransmitter concentration sensor (WINCS) system to monitor real-time neurochemical release in vivo. WINCS relies on fast-scan cyclic voltammetry (FSCV) and constant potential amperometry (CPA) to detect in vivo neurochemical release. In addition, we have developed the Mayo Investigational Neurostimulation Control System (MINCS) to provide wirelessly controlled neurostimulation through four channels. In this chapter, we will review the scientific basis of wireless electrochemical recordings and how these technologies are improving our understanding of the mechanism of DBS and ultimately the care of patients undergoing DBS.

ELECTROCHEMISTRY

Monitoring neurochemicals release in experimental animals has been dominated by two general techniques: microdialysis, which provides excellent selectivity and sensitivity; and voltammetry, which exhibits superior temporal and spatial resolution. In

microdialysis, the extracellular fluid in the brain is sampled by slowly flowing a physiologic solution (such as sodium phosphate buffered saline) through an implanted semipermeable tubing and collecting the resulting solution containing molecules of interest. This dialysate is analyzed *ex vivo* using sophisticated analytical methods such as chromatography, electrophoresis, electrochemical detection, laser-induced fluorescence, and mass spectrometry [5–7]. In contrast, voltammetry measures analytes directly at an implanted probe using electrochemical oxidation and reduction techniques. FSCV is used for direct measurement of electroactive neurochemicals at a carbon fiber microelectrode (CFM), whereas CPA is typically used for measuring non-electroactive neurochemicals via a biosensor [6, 8–11].

Electroactive neurochemicals, such as dopamine, norepinephrine, serotonin, adenosine, nitric oxide, and histamine, are directly oxidized and/or reduced at the CFM [6, 8, 12]. Non-electroactive neurochemicals are measured indirectly using an electrochemical biosensor, which incorporates a chemical recognition element that acts on the analyte [9, 10]. The result of this interaction is electrochemically interrogated. For example, for glutamate, the chemical recognition element is the enzyme glutamate oxidase, which catalytically produces hydrogen peroxide in proportion to the concentration of glutamate. The hydrogen peroxide is subsequently oxidized by CPA. CPA can be performed by applying a fixed potential of +0.8 V with a data acquisition rate at 10 k samples/s [13, 14]. FSCV for electroactive neurochemicals can be performed by linearly scanning the applied potential between –0.4 and +1.0 to 1.5 V at a rate of 300 to 400 V/s. Potential scans may be repeated at 100 ms intervals, with the CFM resting at a bias of –0.4 V during the time between voltage excursions. Data are usually acquired only during the scan and at a rate of 100 k samples/s.

A CFM is used for these electrochemical measurements since some of the compounds of interest, for example dopamine, adsorb onto the carbon surface, allowing the electrochemical oxidation or reduction to occur maximally with changes in the applied voltage. A CFM is typically fabricated by inserting a single carbon fiber ($r = 2.5\ \mu\text{m}$) into a borosilicate capillary tube, then heated and pulled to a tapered microscopic tip using a standard pipette puller [15]. The sensing portion consists of

the exposed carbon fiber, which is trimmed so that it extends approximately 50–100 μm beyond the glass insulation. An Ag/AgCl electrode is commonly used as a reference electrode and consists of a 30 ga. chloridized silver wire. Conventional glass-insulated CFMs with smaller length carbon tips (e.g., 5–10 μm) enable high spatial resolution and minimization of tissue damage. However, these electrodes are too fragile and thus are not suitable for acute and chronic human recordings. In 2012 the Mayo Clinic Neural Engineering Laboratory developed a safer and more durable electrode for human use. Made of carbon fiber insulated with polyimide and fused silica, the electrode has a 7 μm diameter sensing tip and a 110 μm shaft. These electrodes have successfully been utilized for acute human recordings and became the basis of a flexible electrode for chronic implantation. This implantable chronic electrode allows neurochemical sensing, enabling both long-term studies of the neurochemical mechanism of DBS and creating the potential for closed-loop systems based on real-time neurochemical feedback. Used in large animal (swine) models, we have investigated its efficacy in detecting robust stimulation-evoked dopamine release (10–15 nA) in the nucleus accumbens of swine over a period of 35 days.

Principles of CPA and FSCV

All electrochemical techniques are based on the general principle of applying a voltage to an electrode and monitoring the resulting flow of current [6, 8]. These measurements are quantitative, because the current is related to analyte concentration. CPA and FSCV differ in how the electrode potential is applied. In CPA the potential is fixed, whereas in FSCV the potential is linearly scanned [6, 8]. Figure 19.1a shows the relationship between applied potential (top) and current resulting from the oxidation and reduction of dopamine measured at a CFM (bottom) during a single scan in FSCV. Current is plotted relative to time, and each time point corresponds to a specific voltage in the scan. This current trace has been corrected for the large background current recorded at the CFM during a scan by a subtraction process (i.e., background subtracted). The positive-going current peak recorded during the positive phase of the voltage scan is the result of dopamine oxidizing (i.e., electron loss) to form dopamine-

ortho-quinone. The negative-going current peak recorded during the returning negative phase is the result of reduction (i.e., electron gain) of the electroformed quinone. When current is plotted against voltage instead of time, this relationship is called a voltammogram (Fig. 19.1b, bottom), which serves as a chemical signature for identifying the neurochemical detected.

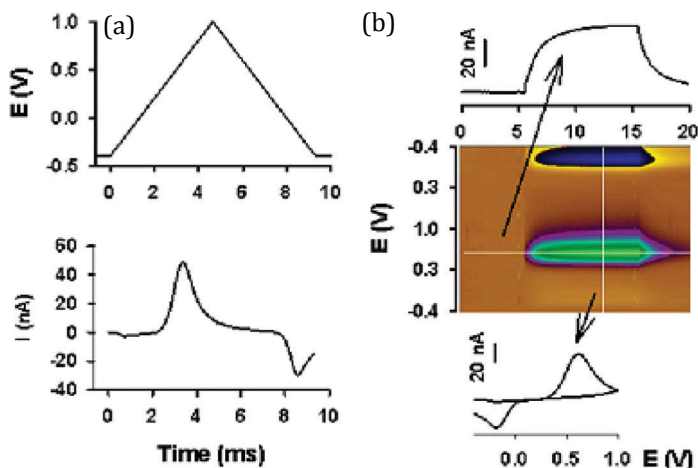


Figure 19.1 Principles of FSCV. (a) The relationship between applied potential (top left) and the induced dopamine oxidation (~3 ms) and reduction (~8.5 ms) current (bottom left). (b) Temporal plot of dopamine oxidation current recorded in a flow cell in vitro (top right) and as a pseudo-color plot (middle right). A voltammogram shows the relationship between applied voltage and induced current (bottom right).

Since the voltage scan is repeated at 100 ms intervals, these current traces can be temporally aligned to reveal dynamic changes in neurochemical concentrations, as shown in the pseudo-color plot of an in vitro experiment in Fig. 19.1b. The x-axis represents the time of the applied scan, the y-axis is the applied potential, and the z-axis is measured current (color). The brown color represents zero current after background subtraction. Two color features emerge at approximately 6 s, which correspond to the addition of dopamine. The greenish-purple feature at approximately +0.6 V is dopamine oxidation to the quinone, whereas the yellow-purple feature at -0.2 V is the resultant quinone reduction to dopamine. A vertical line

through these features permits determination of the background subtracted dopamine voltammogram shown below the pseudo-color plot. Here, the voltammogram is “folded” (i.e., current plotted relative to potential) instead of “stretched” (i.e., current plotted relative to time). A horizontal line across the zenith of the dopamine oxidative peak yields the dynamic change in dopamine current with time shown above the pseudo-color plot. This measured current can be converted to concentration by calibration of the CFM electrode in known concentrations of dopamine.

Compared to the probe used for microdialysis, the CFM used here is considerably smaller (5 μm diameter, 50–100 μm length) and causes minimal implantation damage [16, 17]. Both voltammetric techniques described also exhibit superior temporal resolution [6, 8]. Typically supporting 100 ms resolution, FSCV is slower than CPA because sufficient time must be allowed to collect individual voltammograms but unlike CPA serves to identify the analyte detected. In contrast, CPA supports monitoring as fast as data acquisition permits, dependent upon diffusion equilibrium with the electrochemical sensor, because the analyte is chemically oxidized by the enzyme as soon as it comes in contact with the sensor. While CPA with microsecond resolution has been used to capture single vesicular release events from individual cells [18, 19], slower sampling, typically between 1 and 16.7 ms, is sufficient for *in vivo* neurochemical monitoring [20, 21]. Because of the detection scheme, even slower CPA measurements (100 ms) are sufficient for enzyme-linked biosensors [22].

Wireless Instantaneous Neurotransmitter Concentration System (WINCS)

As mentioned in the introduction, WINCS was developed for neurochemical monitoring during functional neurosurgical procedures [23, 24]. A small, battery-operated device, WINCS performs electrochemical measurements at a brain-implanted microsensor and wirelessly transmits collected data to a base station by means of Bluetooth® telemetry (Fig. 19.2). It supports both FSCV and CPA. The fact that it has a compact profile, is battery powered, and uses digital telemetry makes WINCS particularly attractive for intraoperative neurochemical monitoring in a crowded, electromagnetically noisy surgical arena.

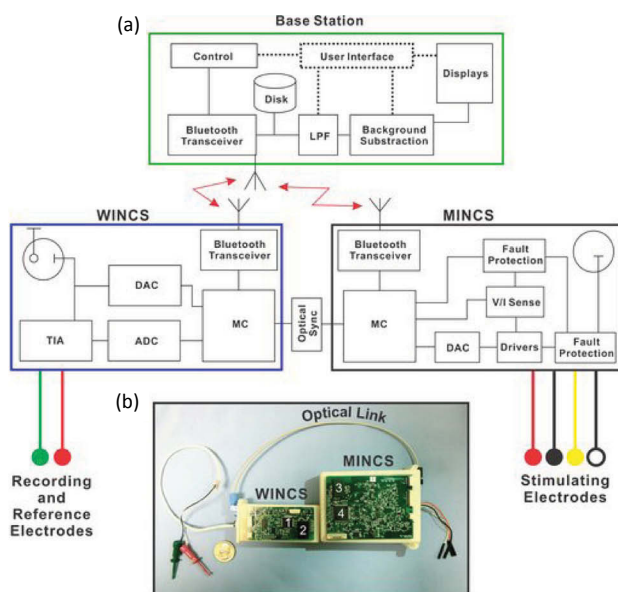


Figure 19.2 WINCS-MINCS Hardware. (a) Schematic representation of the computer base station, WINCS, and MINCS. The neurochemical recording device, WINCS, and the synchronized stimulator, MINCS, are linked via an optical connection. Both units connect wirelessly via Bluetooth technology to a base station, which commands both systems via WincsWare software. Leads from each device provide connections to the recording and reference electrodes (red and green circles) and 4 stimulating electrodes (red, black, yellow, and white circles). (b) Photograph of the MINCS-WINCS hardware showing relative size, optical connection, and recording and stimulating electrode leads. ADC = analog-to-digital converter; DAC = digital-to-analog converter; LPF = low-pass filter; MC = microcontroller; TIA = transimpedance amplifier; V/I Sense = voltage/current sense. Numbers 1 and 4 indicate the microcontrollers; 2 and 3 are the Bluetooth modules.

Connected by lead wires to the microsensor and reference electrode, WINCS is enclosed within a sterilizable, hermetically sealed polycarbonate case during its operation. The WINCS base station computer records, processes, and presents the transmitted data in real-time. All WINCS operations are wirelessly remotely controlled by the base station, which can be situated some distance from the WINCS device within Bluetooth range. However, the

base station's Bluetooth transceiver can safely be more remotely connected to the base-station computer via a USB cable allowing further separation of the computer from the patient. During MRI, the WINCS unit can also be positioned inside the MR scanner room within 3 to 5 m of the base-station transceiver, a distance well within the nominal 10 m range of class 2 Bluetooth transmitters.

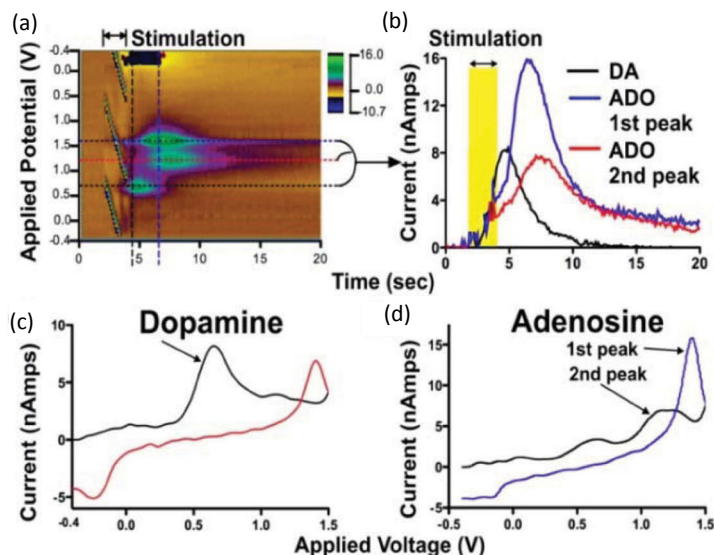


Figure 19.3 FSCV of Dopamine (DA) and Adenosine (ADO) Release in the Caudate of the Swine. (a) STN DBS (3 V, 120 Hz, 0.1 ms pulse width for 2 sec) evoked both DA and ADO release. The color plot shows the appearance of DA release immediately during and after stimulation, while the peak corresponding to ADO release was delayed. (b) Current versus time plot at +1.5 V, +1.0 V, and +0.6 V showing ADO (blue and red) and DA (black line) release following electrical stimulation (yellow box). (c) and (d) Background subtracted voltammograms for DA and ADO, respectively, demonstrate the measurement of both DA and ADO release (black and blue vertical dashed line in (a)). The black lines indicate currents generated by forward-going potentials, and colored lines indicate currents generated by reverse-going potentials.

We have demonstrated that WINCS can measure real-time oxygen, dopamine, adenosine, and serotonin concentrations in

vivo using CFMs and glutamate release using an enzyme-linked biosensor during DBS [23–27]. For these experiments, we implanted a CFM into the head of the caudate nucleus of isoflurane anesthetized swine, and FSCV recordings were taken during brief (2 s) electrical stimulation applications using a Medtronic human DBS electrode implanted in the ipsilateral subthalamic nucleus (STN). With HFS (120 Hz) mimicking clinical DBS frequencies, adenosine and dopamine were clearly released (Fig. 19.3a). The temporal pattern and magnitude of release of dopamine (black line) and adenosine (blue and red line) evoked by STN DBS are shown in Fig. 19.3b. The voltammograms obtained with WINCS-based FSCV in the swine revealed one peak at +0.6 V for dopamine oxidation and two oxidation peaks for adenosine (first peak near +1.5 V and second peak near +1.0 V) as shown in Figs. 19.3c,d, respectively.

Untethered Neurostimulation System: Mayo Investigational Neurostimulation Control System (MINCS)

In order to provide a wide range of stimulation parameters, nonuse of line current, and coupling with the WINCS unit to eliminate stimulation artifact which interferes with neurochemical detection, we developed MINCS, which is capable of providing wirelessly controlled neurostimulation [28]. Like WINCS, MINCS is controlled by in-house designed base station software, WincsWare which allows the operator to easily define pulse amplitude, frequency, duration, polarity, and pulse-train pattern at the stimulation electrode. This flexible programming provides the application of both clinical DBS parameters and investigational parameters. Using a combined system in which MINCS and WINCS communicate through an optical fiber sync (Fig. 19.2), Chang et al. stimulated the medial forebrain bundle of anesthetized rats and showed evoked striatal dopamine release. Similarly, STN HFS has been shown to elicit dopamine and adenosine release distally in the striatum of isoflurane anesthetized swine. In these experiments, electrochemical techniques were able to evoke, identify, and record dopamine release without interference from the electrical stimulation pulses (Fig. 19.4).

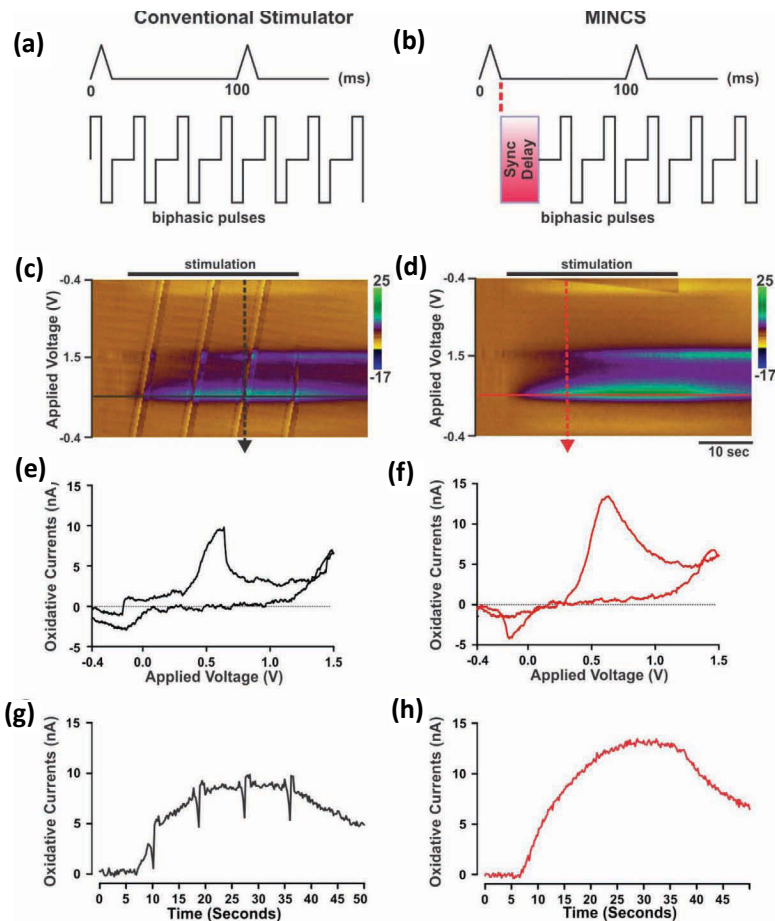


Figure 19.4 Elimination of Stimulus Pulse Artifacts using MINCS-WINCS Synchronization. (a) and (b) Diagrams comparing the stimulus pulse sequences provided by a conventional stimulator (left) and MINCS (right) in relation to FSCV scans (pyramidal waveforms). Optically synced with WINCS, MINCS eliminates stimulus pulse interference with FSCV measurements by imposing a delay after every scan. (c) and (d) Comparison of color plots of striatal dopamine release acquired in vivo from medial forebrain bundle stimulation (30 second stimulation at 60 Hz, 200 mA, 2 ms biphasic pulse duration) in the anesthetized rat with (right) and without (left) stimulus pulse synchronization. Stimulus pulse artifacts are readily apparent as repeating diagonal bands

in the color plot (left). (e) and (f) Cyclic voltammograms recorded at the peak of stimulation-evoked dopamine release (right; dashed red arrow in (d)) and coincident to stimulus pulse interference (left; dashed black arrow in (c)). Note the marked distortion of the voltammogram recorded during the occurrence of a stimulus pulse. (g) and (h) Time courses of stimulation-evoked changes in dopamine oxidation current extracted from each respective color plot record at the applied voltage of +0.6 V (right, solid red line in (d); left, solid black line in (c)). Stimulus pulse artifacts (negative-going spikes in current) were readily apparent using a conventional stimulator, while entirely absent using MINCS.

To monitor real-time neurochemical changes associated with DBS in human patients, WINCS-based FSCV measurements were performed in the ventral intermediate (VIM) nucleus of the thalamus in patients with essential tremor, all of whom were awake during DBS neurosurgery (Fig. 19.5; [29]). Arm and hand tremor were measured using a wireless three-axis accelerometer which patients held in the hand opposite to the implanted hemisphere. Upon implantation of the DBS electrode, but prior to activation of the pulse generator, tremor amplitude was significantly reduced, presumably an outcome of the “microthalamotomy effect.” Coincident with tremor reduction, DBS electrode implantation evoked a large increase in the FSCV oxidation current peak at $+1.45 \pm 0.03$ V, corresponding to adenosine oxidation. During DBS stimulation, similar FSCV measurements (-0.4 to $+1.5$ V every 100 ms) were found in the VIM thalamus (Fig. 19.5a–c). An FSCV color plot (Fig. 19.5d) revealed that during DBS, an oxidation peak current was detected at $+1.4$ V, corresponding to adenosine oxidation [30–32]. Although a handheld accelerometer to measure tremor is not shown in Fig. 19.5, the rise in the adenosine signal during and after DBS was visually observed (and confirmed via time encoded video recording) to correlate with a marked reduction in tremor.

The combination of WINCS and MINCS is the prototype for a fully implantable integrated system of neurochemical detection and real-time controllable stimulation system, thereby providing a closed-loop DBS system.

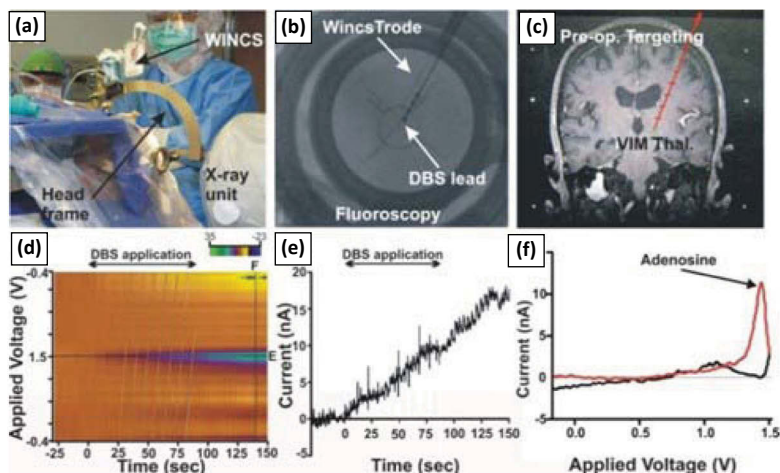


Figure 19.5 Neurochemical Changes Evoked by DBS in the VIM Thalamus in an Essential Tremor Patient. (a) Surgical setup. (b) X-ray showing the position of the WincsTrode and DBS lead in the VIM. (c) MR image of implantation trajectory. (d) Pseudo-color plot showing the appearance of oxidation current at +1.4 V upon application of DBS (135 Hz, 60 μ s pulse width, and 0.5–2.0 V, incrementally increased). (e) Current versus time plot at +1.4 V following DBS. Note stimulus artifacts during DBS application. (f) Background subtracted cyclic voltammogram showing the oxidation peak of adenosine at +1.4 V. The black line indicates oxidation currents generated by forward-going potentials, and the red line indicates oxidation currents generated by reverse-going potentials.

CONCLUSION

The use of FSCV for the detection and quantification of neurochemical release during DBS provides real-time neurochemical data. This neurochemical recording capability can serve to elucidate critical underlying biological mechanisms of DBS. The capacity to detect and quantify in real-time changes in neurochemical concentrations in the brain during DBS in humans could serve as the foundation of the development of chronically implanted closed-loop DBS systems. Future directions include confirmation of chronic biocompatibility, software for closed-loop control, power, and miniaturization appropriate for implant and monitoring of

resultant activity in human patients. These advancements and improvements in DBS hardware and software could also broaden the range of neurological and psychiatric conditions that can be treated by DBS. Whether next-generation “smart” DBS devices will utilize continuous neurochemical feedback is unknown, but such technologies will undoubtedly have a profound impact on both basic and clinical neuroscience.

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Chapter 20

Electrodes for Neural Stimulation and Monitoring

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INTRODUCTION

Electrodes used in neural stimulation and monitoring serve a crucial role as the point of interface between an engineered electronic system and natural biological tissue. While an electrode may be as simple as a section of exposed conductive material, in practice, an array of considerations constrain the engineering of practical neural electrodes. Among these considerations are size and shape, current density, electronic impedance, surface chemistry, material biocompatibility, lifetime/longevity, and surgical practicality of installation and removal.

Electrodes also differ relative to their intended use, which defines the direction of electrical current and information flow. Some electrodes are purely passive and serve only to monitor and record endogenous voltages (signals). In such cases, current and information flows from the biological tissue through the

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electrode to the electronic system. Other electrodes are designed for application of voltage (and therefore current) from the electronic system to neural tissue for the purpose of stimulation. Finally, there are electrodes designed to serve both purposes or to serve a hybrid purpose. For example, in fast-scan cyclic voltammetry (FSCV), a small transient voltage is applied for the purpose of monitoring neurotransmitter concentration via oxidation/reduction chemistry, measured by current flow. Here, the electronic system applies a voltage to a carbon-based electrode within neural tissue, for diagnostic and monitoring purposes rather than for the purpose of neural stimulation.

ELECTRODE DESIGN CONSIDERATIONS

Electronic Implications of Design

The most obvious differences between neural electrode designs are the construction material and the size and shape of the overall electrode and its individual electrical contacts. Electrodes differ in the number of distinct (electrically isolated) contacts or “channels” they contain: generally from one to dozens. The greater the number of channels or contacts, the greater the number of distinct areas of the brain or of an individual nerve (contiguous volume) they can stimulate or monitor. However, electrodes with more channels are necessarily larger and thus more difficult to implant and more disruptive to the host tissue. Electrodes with many channels are also more difficult to fabricate than single channel electrodes and require more complex wiring harnesses, connectors, and interface electronics.

Each distinct electrically isolated channel of an electrode is associated with an electrical conductor which interfaces electrically with the neural tissue. The size of this conductor impacts the size of the area of neural tissue in contact with the electrode, and hence the volume of associated tissue stimulated or sampled and the spatial precision of the stimulation or monitoring. Electrode sizes can vary from the low single-digit micrometers (10^{-6} m) to low single-digit millimeters (10^{-3} m). Electrodes at the smaller end of this spectrum are capable of interacting with individual neurons but tend to be very fragile, short-lived, and yield very

weak (high impedance) signals that are suitable only for monitoring or research use. Electrodes at the larger end of this spectrum are more robust and more suited for chronic surgical implantation into patients for purposes of stimulation.

The size (area) of an electrode also affects its electrical properties. In the case of stimulating electrodes, larger electrodes deliver current over a larger area, thus decreasing the “current density” (the number of electrons flowing between the electrode and the tissue per unit area per unit time). This is important because high-current densities may damage the electrode, the neural tissue, or both. In engineering and regulatory practice, various empirical safety limits on current density are observed, such as that published by Shannon [1]. On the other hand, excessively large electrodes may stimulate too large a volume of tissue, leading to undesirable off-target effects. However, advanced stimulation electrodes can be made to apply different voltages to a patterned array of channels so as to “steer” the resulting electrical field in a defined way. This technique can be used to refine the exact volume that is subject to stimulation [2].

Monitoring/recording electrodes, on the other hand, are faced with a problem on the opposite (small-signal) end of the spectrum. The amount of electrical charge produced endogenously by the brain or other neural tissue is comparatively small. That is, as a high-impedance voltage source, it cannot deliver a large current. An excessively large monitoring electrode would act as a capacitor, thus requiring too much charge to change its potential, leading to a slow dynamic response and temporally ambiguous data (i.e., the electrode would act as a low-pass filter). Additionally, large electrodes monitor a large number of neurons with potentially heterogeneous behavior, leading to spatially ambiguous data. On the other hand, excessively small electrodes lead to higher impedance (as well as higher thermal noise) which reduce data quality [3].

Electrodes are also commonly formed into multi-conductor arrays so as to monitor or introduce electric potentials over a grid of points. By recording voltages at several adjacent points in the grid, triangulation can be used to estimate the position of individual active neurons—even if the neuron in question is not in direct contact with one of the grid point contacts.

Biological Considerations: Acute and Chronic

Since the electrode is the point of contact between delicate neural tissue and the engineered electronic device, the electrode must be designed so as not to cause excessive damage or disruption for the length of time that it is present. These considerations become particularly important in chronic electrode implantation.

In acute electrode placement, the primary consideration is acute injury to the brain or nerve tissue. For example, implanting a deep brain stimulation (DBS) electrode requires the careful selection of an insertion path so as to avoid disrupting blood vessels and other functionally important regions of the brain. Clinically, this is accomplished with the aid of a brain atlas and magnetic resonance images of the patient's brain to select an electrode insertion trajectory.

In chronic electrode design, additional considerations come into play. For example, the brain or nerve tissue is not entirely stationary with respect to the skull due to pulsation of the circulatory system and the resumption of normal movement following surgery. Additionally, brain and nerve tissue is soft, with a Young's modulus in the range of 0.1–1.5 kPa, which is similar to jelly [4–8]. To prevent irritation to the delicate neural tissue, electrodes should be designed using the softest, most elastomeric (lowest Young's modulus) materials that are practical. The use of metal, while critical as an electrical conductor, should be minimized. In addition to being inelastic, metallic parts of electrodes can also interfere with magnetic resonance (MRI) scans. Common materials for the construction of electrode bodies (the non-conductive parts) are parylene, polyimide, silicone polymers (e.g., PDMS), fluoropolymers (e.g., PFA), and others. Sharp edges must also be avoided where possible. Any anchorage between the electrode and the skull must also be somewhat flexible, so that the electrode body can move with the brain so as to avoid inflammation of and damage to the neural tissue or damage to the electrode.

Even with a well-designed electrode, however, penetration of nerve tissue will tend to lead to formation of a "glial scar" that encapsulates the penetrating electrode and acts as a local electrical insulator, thus isolating the electrode from the neurons that it is designed to record or stimulate. This reaction can lead to

failure of an electrode over time, even if that electrode functioned well immediately following insertion, and even if the electrode itself is functioning normally [9]. This is especially true even under ideal conditions in the case of recording electrodes, which usually are of a higher impedance design than stimulating electrodes. In the case of stimulation electrodes, the increase in impedance can be overcome by increasing the stimulation voltage. In the FSCV electrode (see Chapter 18 for more details on FSCV), the glial scar increases the time constant of the electrode area reaching equilibrium with the surrounding active neural tissue.

Finally, the electrode should not exert excessive pressure on the brain or nerve tissue once the surgical wound is closed. Pressures exceeding 2.5–8.0 kPa or strain exceeding 8–15% should not be exceeded, as this can limit blood perfusion and flow [10, 11]. Additionally, the brain is delicate and subject to mechanical stimulation, which can produce effects similar to electrical stimulation.

Surface Chemistry and Materials

As a general rule, an ideal electrode will not itself undergo electrochemical reactions across the voltage range it is subjected to, and electrode materials should be selected with this in mind. Independent of their electrochemical behavior, electrode materials must also be inert within the body and must not chemically degrade when exposed to the water, salt, protein, etc., of tissue. Electrochemical reactions within the tissue are generally unavoidable. For instance, above a potential of about 1.5 V, water will be separated into hydrogen and oxygen (electrolysis) at the electrode surfaces, thus providing small quantities of reactive species (such as oxygen and hydroxide ion) that can contribute to electrode corrosion. Short of limiting the applied voltage, reactions of this type cannot be avoided.

Common electrode materials that are in wide use are the noble metals, such as gold, platinum, platinum-iridium alloys, as well as tungsten. These metals tend to be inert across a range of common voltages. Carbon (in various allotropes) is also coming into use for neural electrodes, particularly for FSCV, because it is relatively inert over the wide range of positive and negative potentials encountered in that technique. Silicon is also used

in some electrodes due to the wide variety of techniques (borrowed from the electronics industry) available for etching and coating it. However, it is also a very hard and brittle material. Modification of surfaces and surface chemistry is the next logical extension of stimulation electrodes. These coating materials include allotropes of carbon (such as graphite and diamond), polymer surfaces, such as conductive polymers, hydrogels, and biologically active compounds) [12].

In addition to the material chosen for the electrode, the applied voltage has a strong impact on the chemistry that may occur at the electrode surface and within the adjacent tissue. Almost any electrode material, no matter how inert within some range of voltages, will become reactive outside that range. Since an accurate *ab initio* prediction of the complete chemical behavior at an electrode surface is quite difficult, laboratory tests to check for corrosion are required before using a novel electrode material or before using an established material outside its established voltage/current range. As a general rule, the higher the applied voltage, the wider the variety of (generally undesirable) chemical reactions that are thermodynamically possible at the electrode surface. Higher currents will tend to increase the rates of those reactions. Finally, electrochemical reactions are temperature-dependent, although this is rarely an issue *in vivo*, where temperature is closely regulated by homeostasis.

Wiring and Connectors

The wiring and proximal electronic connector of the neural electrode must also be considered in design. While these components are not as intuitively important as the distal end of the electrode that interfaces directly with the neural tissue, they nevertheless can introduce problems if neglected in the engineering process.

The wiring may be called upon to penetrate membranes (e.g., the meninges or perineurium), and such penetrations must be kept as small as possible. Leads must also be surgically tractable, that is, flexible enough to route, but sturdy enough to withstand the process of implantation. Leads for monitoring small signals must also be kept as short as possible with the largest possible conductors to avoid introducing excessive

electrical impedance and noise into an already-weak signal. Many of these requirements are contradictory, so intelligent trade-offs must be made to arrive at an optimal design.

It should also be remembered that unshielded wires act as antennas. In the case of monitoring/recording leads carrying small signals, this may lead to electrical noise (spurious voltages) in the recorded signal. In a worst-case scenario, a patient in the presence of a very strong time-varying electromagnetic field (e.g., from a nearby radio transmitter or an MR scanner) could theoretically experience unintended neural stimulation with unpredictable results—regardless of whether the electrode was originally intended for stimulation or recording. Keeping leads short and electrically shielded may help prevent this. Various techniques of twisting the conductors can also help mitigate the problem of induced voltages. For more information on antennas and shielding, consult a specialist text on electrical (particularly radiofrequency) engineering. New lead designs intended for chronic implantation should be tested to characterize their behavior in the presence of strong radio frequency radiation.

NEURAL ELECTRODE EXAMPLES

Any practical electrode design must balance the various considerations mentioned above. The particular designs discussed below illustrate the ways in which different engineers have approached these issues and arrived at different electrode designs intended for different purposes.

Medtronic 3387 and 3389 Deep Brain Stimulation Electrodes

The Medtronic 3387 and 3389 DBS electrodes are commercially available and currently in clinical use for chronic implantation into patients (Fig. 20.1). These electrodes are intended for stimulation rather than monitoring. They contain four independent channels and are relatively large. The electrode shaft is 1.27 mm in diameter with four platinum-iridium contacts at the distal end. The contacts are annular, 1.5 mm in length, and they are spaced 1.5 mm (model 3387) or 0.5 mm (model 3389) apart.

The insulating components are made of various biocompatible polymers with the “shaft” of the electrode primarily composed of silicone rubber. This makes the electrode pliable so as to avoid damage to the brain, while a removable metal “stylet” runs down the central axis of the electrode to make it stiff enough for surgical implantation. The four electrical conductors inside this shaft are twisted in a helical pattern so as to reduce the possibility of electrical interference.

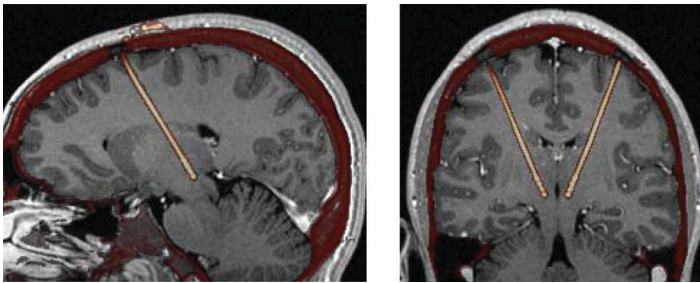


Figure 20.1 A composite of MRI and CT images of DBS electrodes implanted bilaterally in the thalamus of a patient with Tourette syndrome. These electrodes (manufactured by Medtronic and discussed in detail later in this chapter) contain four annular platinum-iridium contacts within the last centimeter of their distal ends. They are connected to an electronics package that is implanted in the patient’s chest (not shown).

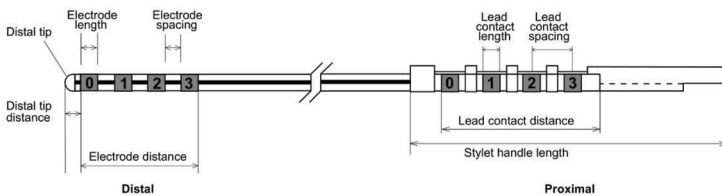


Figure 20.2 Medtronic 3387 deep brain stimulation electrode (image from Medtronic marketing literature).

This electrode is connected to an implantable deep brain stimulation unit that is implanted in the chest. The Medtronic Activa® stimulators that mate to these electrodes produce pulses ranging 0–10.5 V and currents up to 25.5 mA, with polarity being programmatically adjustable.

Electrophysiology Targeting Electrode

Prior to placement of a DBS electrode such as the Medtronic 3387 or 3389, it is common practice to confirm the targeted brain structure with passive electrophysiology recording in the operating room using a disposable electrode such as the D-Zap series by FHC, Inc. (Fig. 20.3). The electrode used for this task is not implanted chronically, but is utilized for a short time intraoperatively to sense neuronal firing activity at its tip. The electronic signal indicating firing of the “correct” neurons is monitored auditorily during electrode insertion and is used to identify the exact location for the chronically implanted DBS electrode. The intraoperative targeting electrode is then removed and the DBS electrode is implanted permanently in the same location (same stereotactic coordinates).



Figure 20.3 Electrophysiology targeting electrode. The exposed tungsten tip is at right (though too small to see at this resolution), the electrical contacts at left. The red contact at left is connected to the tungsten tip, while the white contact at left-bottom is connected to a stainless steel jacket coaxial with the tungsten tip. In use, this electrode is inserted into the brain through a stainless steel cannula, which is held in place by a stereotactic surgical frame. The black scale bar at the lower-right is 1 cm.

Materials of construction for these electrodes include tungsten or stainless steel insulated along their lengths with only a small tip exposed. These cores are often on the order of a few hundred micrometers in nominal diameter, sharpened to a fine point. A stainless steel sheath (electrically insulated from the interior sensing electrode) is used as a counter-electrode and as protection for the thin interior electrode core.

Since these electrodes are only used for a few minutes during surgery, wiring is temporary and provided by clip-leads similar to those used in electronics laboratories.

Utah Multi-Electrode Array

The Utah Array is a relatively well-known recording and stimulating electrode array originally developed at the University of Utah and produced commercially by Blackrock Microsystems, Salt Lake City, Utah (Fig. 20.4). Many different versions of this array have been produced, but all are on the order of about 0.5–4.0 mm square and contain on the order of 100 distinct channels. The bulk of the electrode is made from a silicon wafer that is sawed, etched, and processed using techniques borrowed from the semiconductor industry. The individual needles (channels) are insulated with polyimide, with only their tips exposed (via chemical etching) [13]. These arrays are currently available, but their use is limited to experimental work.

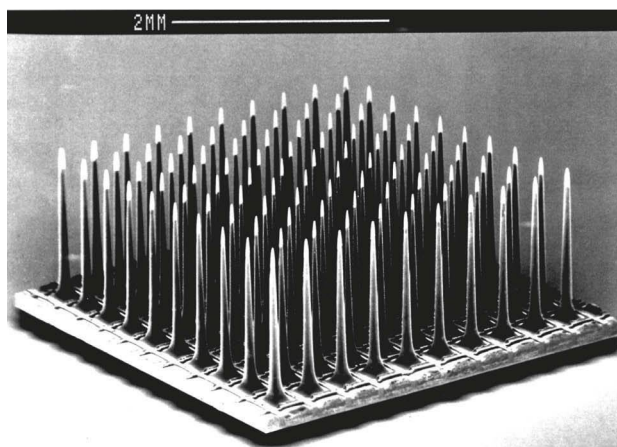


Figure 20.4 The Utah neural electrode array (at 30× magnification). The bulk of the array is made from etched silicon, with glass (fused frit) and parylene comprising the insulating portions.

Carbon Fiber Fast-Scan Cyclic Voltammetry Electrode

FSCV is a powerful analytical method that places unique demands on an electrode (see Chapter 18 for more details on FSCV). While the technique involves the application of a small voltage to the electrode, the intent is not to supply sufficient voltage or current to produce neural stimulation. Rather, the voltage causes chemical oxidation/reduction reactions in neurotransmitter

and other molecules near the electrode surface. Since these redox reactions occur at specific voltages for specific molecules, the amount of current drawn at a particular voltage (the I - V curve, in the electrical engineering parlance) can be used to infer the concentrations of specific molecules at the electrode.

Because the voltages and currents are small (on the order of 100 μ V and 100 μ A), and because the applied waveform is alternating rather than direct current (typically a pulsed triangular wave above a non-zero negative baseline), the complex impedance of the electrode and cable must be considered. Given the small signals involved, it is possible for capacitive “charging current” to overwhelm and mask the small current drawn by the redox chemistry.

Additionally, because endogenous concentrations of neurotransmitters are so small, it is important to consider the effect of electrode material on sensitivity. Certain materials, such as gold (or other metals) may be chemically inert, but they generally do not adsorb molecules of the analyte of interest (such as dopamine) on their surface, thus producing a relatively weak signal [14]. Carbon provides a surface with favorable neurotransmitter adsorption characteristics leading to enhanced sensitivity, so it is the material of choice in neural FSCV electrodes [15].

Laboratory *in vitro* carbon fiber FSCV microelectrodes have been fabricated from carbon fiber, often the exact same material used to construct carbon fiber components for aircraft, bicycles, etc. Since these electrodes are not commercialized, but are built as-needed in the laboratory, the particulars of their designs (dimensions, insulation and structural materials, etc.) differ widely. An example electrode for acute studies is depicted in Figs. 20.5 and 20.6. These electrodes cannot be used for chronic implantation in humans due to the fragility of thin carbon fibers, but they have been used extensively in acute and chronic animal studies and limited acute human studies [16].

An example of a modern carbon fiber-based chronic FSCV electrode used for large-animal studies at the Mayo Clinic Neural Engineering Laboratory can be seen in Fig. 20.7. This electrode is designed to be used in conjunction with the Wireless Instantaneous Neurotransmitter Concentration System (WINCS) [17–22].

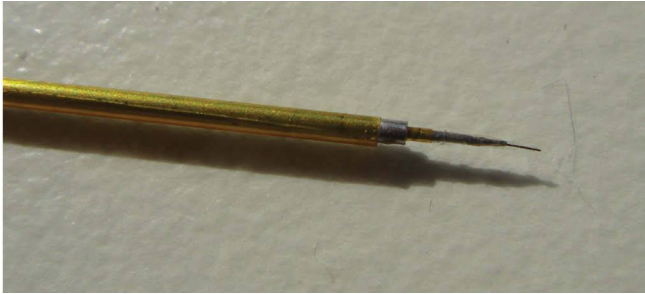


Figure 20.5 Carbon fiber electrode constructed by the Mayo Clinic Neural Engineering Laboratory. The exposed carbon fiber tip is at right.

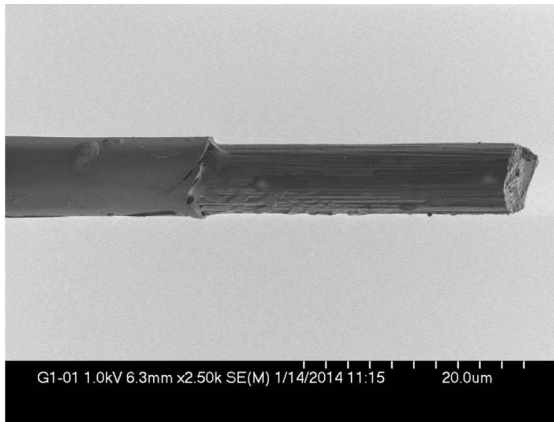


Figure 20.6 Scanning electron micrograph of a carbon fiber electrode tip (at right) with glass insulation (at left).

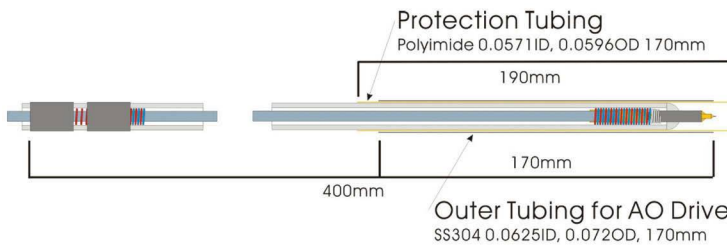


Figure 20.7 Carbon fiber electrode for fast scan cyclic voltammetry recording designed at Mayo Clinic. The carbon fiber for analysis is at the right (distal) end.

The electrode in Fig. 20.7 consists of a carbon fiber with a diameter on the order of 10 micrometers (of the type commonly used in the aerospace industry) held in place inside a small silica tube. This tube is secured inside an annular stainless steel counter-electrode, while supporting non-conductive structures are made of polyimide (internally) and silicone rubber (externally, in contact with tissue). The leads are stainless steel and are wound helically inside a silicone rubber tube. The electrode is fabricated with a Nitinol wire stylet running down the center of the lead (much like the Medtronic 3387 and 3389). This stylet is removed during the implantation surgery after the electrode is placed. After the stylet is removed, the remaining structure is flexible and able to move and flex in order to accommodate motion of the brain inside the skull.

While the number of electrodes that have been developed for research and clinical use is enormous, these few examples illustrate the key issues that engineers and scientists must consider when designing electrodes to introduce voltages into neural tissue (stimulation) or record signals from tissue (electrophysiology and FSCV).

SUMMARY

As the clinical use of neuromodulation techniques expands, so too will the need for advanced neural electrodes. Not only will new electrodes for neural stimulation be required, but new techniques of neuromodulation (such as closed-loop deep brain stimulation, which requires monitoring and recording brain activity) will require fundamentally different electrode designs than those currently used in clinical practice. As work on this field progresses, engineers will be forced to address the various inherent design trade-offs between neural stimulation and the recording/sensing of neural activity. The current state-of-the-art in clinical practice is limited primarily to platinum/iridium electrodes and fairly large contact areas, but this will inevitably change as the limits of sensitivity, longevity, and tissue compatibility are encountered.

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Chapter 21

Closed-Loop Control Systems for Deep Brain Stimulation Therapy

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INTRODUCTION

Deep brain stimulation (DBS) is a surgical treatment for movement and psychiatric disorders that achieves therapeutic benefit through the delivery of high-frequency electrical stimulation (typically 100–130 Hz) to specific brain regions associated with pathological activity [1–3]. Sustaining these therapeutic effects over time while minimizing stimulation-induced adverse effects requires periodic manual adjustment of stimulation parameters [4]. As such, clinical DBS programming is an iterative, time consuming, and expensive process [5, 6]. During a programming session, active electrode contacts, as well as stimulation frequency, amplitude, and pulse duration are empirically adjusted through a process that depends on the subjective experience of the patient, acute clinical observations, and the clinical experience of the programmer. Additionally, only a limited subset of

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the stimulation parameter space can be explored in a given programming session. As a consequence, many DBS patients require several months of regular parameter adjustments following implantation of the DBS system before an optimal balance between therapeutic benefit and adverse effects can be achieved [7–12]. These parameter adjustments are further complicated by the dynamic and comorbid nature of most neurologic and psychiatric disorders.

The limited stimulation parameter space that can be explored clinically, coupled with the subjective nature of the parameter adjustments underscore the need for better alternatives to clinical DBS programming. One alternative is the use of closed-loop systems that continuously monitor the dynamic environment within the brain and respond by automatically adjusting stimulation parameters to achieve and sustain optimal therapeutic efficacy [13–15].

This chapter explains how real-time neurochemical and electrophysiological feedback signals coupled with insights from functional imaging techniques could be used to implement a feedback-controlled DBS system capable of sustained, optimal patient-specific therapeutic benefit. Although behavioral feedback (e.g., motor behaviors like tremor) may also eventually inform a closed-loop feedback system, work to date has been focused on systems that use neural signals, which are thus also the focus of this chapter.

NEUROCHEMICAL BASIS OF DBS

Clinical studies have shown that DBS of the subthalamic nucleus (STN) is associated with up to a 56% reduction in required levels of levodopa, a drug used to compensate for dopamine loss in patients with Parkinson's disease (PD) [16–18]. A relationship between therapeutic DBS and changes in dopamine and adenosine concentration has been observed in both small and large animal models of DBS [19–21]. Specifically, it has been shown that STN DBS evokes dopamine release in the striatum of parkinsonian rats [22, 23]. In addition, studies in swine models of DBS have shown that stimulation-evoked dopamine release is highly correlated with stimulation intensity and frequency [24]. Clinically, adenosine release has been observed during intraoperative

electrochemical fast-scan cyclic voltammetry (FSCV) in patients undergoing DBS of the ventral intermediate nucleus (VIM) of the thalamus for treatment of essential tremor [25]. Combined, these results suggest that stimulation-evoked changes in neurotransmitter release are an important contributor to the therapeutic effects of DBS.

Unfortunately, the specific relationship between stimulation parameters and corresponding changes in neurotransmitter release is not known, nor is the relationship between neurotransmitter release and therapeutic response. Understanding and modeling these relationships is critical for developing closed-loop DBS control strategies capable of predicting the stimulation parameters required to sustain therapeutic benefit by modulating neurotransmitter concentrations [13].

DBS CONTROL PARADIGMS

Existing clinical DBS systems follow an open-loop paradigm in which stimulation parameters are programmed into an implanted DBS device and are held constant until the next programming session. However, this programming paradigm is in conflict with the dynamic nature of the brain and the progressive nature of many disorders treated by DBS. Thus, the positive results from a given programming session may be difficult to sustain for the following reasons: (1) the nature of most neurologic and psychiatric disorders is dynamic and is affected by changes in disease progression and by ongoing environmental and behavioral factors [26–28]; (2) DBS programming relies on subjective evaluation of benefit and adverse effects as well as on the expectations of the patient and clinician; (3) programming is time consuming and allows for the exploration of only a small number of possible stimulation settings in a given session [29–32]; (4) in some neurologic and psychiatric disorders, such as dystonia and depression, the effects of stimulation parameter adjustments on behavior can take up to several months to appear, a delay that can impact outcomes [29–32]. These issues highlight the need for feedback systems capable of quantifying and automatically adjusting levels of stimulation in response to neurochemical, electrophysiological, and behavioral cues.

The ideal closed-loop DBS system would do just that—adjust stimulation parameters in response to internal physiologic feedback, such as electrophysiological and neurochemical activity, as well as to external electromechanical and inertial sensors [13, 15, 33, 34]. Such feedback configurations would eliminate subjective assessments and decrease the need for multiple programming sessions. This improved efficiency in turn would reduce the health care expenses associated with DBS therapy and improve its efficacy, particularly for disorders in which it is difficult to assess or maintain optimal stimulation parameters.

In general, implementation of closed-loop DBS systems requires first that basal and stimulation-evoked neural activity be measured by monitoring physiologic neurochemical and/or electrophysiological signals. Second, neural activity should be mathematically modeled to characterize the causal relationship between electrical stimulation and neuronal activation. Third, a predictive model capable of identifying therapeutic stimulation parameters should be constructed. Lastly, the appropriate brain target should be stimulated with the predicted parameters and the expected and actual responses should be compared (Fig. 21.2).

Efforts to “close the loop” and provide automated adjustments of stimulation parameters are underway. Two types of feedback have been attempted: electrophysiological and neurochemical. Electrophysiological feedback as a means to optimize therapeutic outcome has been attempted in proof-of-principle studies of DBS for treatment of PD [35, 36]. These studies suggest that electrophysiological feedback can improve motor scores by approximately 30% while reducing power consumption by approximately 50% relative to conventional open-loop stimulation strategies. However, clinical outcomes have only been evaluated for selected motor items in the Unified Parkinson’s Disease Rating Scale (UPDRS) [37], and only over short time durations of about 10 minutes.

Electrochemical feedback has also been explored as a way to optimize stimulation in a closed-loop DBS system [13]. This proof of principle study relies on measurement of stimulation-evoked dopamine release in a rodent model of DBS. Grahn and colleagues characterized the mathematical relationship between stimulation-evoked dopamine and DBS parameters and then developed mathematical predictors of stimulation parameters

for achieving control of dopamine levels. This mathematical characterization is critical for developing automated strategies capable of adjusting stimulation parameters in response to a dynamic environment.

REAL-TIME MONITORING OF NEURAL ACTIVITY

As described in the previous section, the first step toward developing a closed-loop DBS device is real-time monitoring of neural activity, which is critical for capturing the dynamic processes taking place within the brain. Real-time monitoring can be performed invasively or non-invasively using electrophysiological signals, neurochemical signals, and functional imaging techniques [24, 38–42]. The following sub-sections describe the most commonly used extracellular neural activity monitoring techniques as well as their implications for the development of closed-loop DBS techniques.

Electrophysiological Monitoring Techniques

Electrophysiological monitoring techniques have been successfully used to study changes in brain activity, such as increased pallidal and nigral activity during STN DBS [38, 40, 43–46]. Electrophysiological monitoring techniques can be characterized according to the spread of activation that they can detect: single-unit recordings, multi-unit recordings, local field potentials, or global field potentials [38, 40, 43–47], each of which is discussed below.

Single and multi-unit recordings

Single-unit recordings capture the activity of single neurons and rely on a high-impedance microelectrode carefully placed close to the body of an individual neuron. The recorded extracellular potentials represent the intracellular action potentials of the nearby neurons [48]. Single unit recordings provide high spatial and temporal resolution [48]. However, the quality of single-unit recordings can be limited by cross-talk from nearby neurons, electrode migration, immune response, and disruption of tissue

surrounding the neuron of interest [49, 50]. These factors can reduce the long-term reliability of single-unit recordings as a source of feedback information.

Multi-unit recordings capture electrical activity from groups of neurons with high temporal and spatial resolution [39, 51, 52]. As such, they provide a more complete representation of neural activity within a target region when compared to single-unit recordings [53]. Unfortunately, multi-unit electrode arrays are stiff, which can lead to shear-induced damage and inflammation of the surrounding tissue. Additionally, currently available electrode arrays allow recording only at the electrode tips, limiting the number and long-term viability of the recorded signals [53, 54].

Local field potentials

Local field potentials (LFPs) are low-frequency electrophysiologic neural signals that reflect the weighted average of synchronous synaptic activity through extracellular space [39, 48, 51, 55]. As such, LFPs describe synaptic activity across anatomic targets of interest over sustained periods of time [35, 54, 56–58]. Thus, LFPs offer great potential for understanding the effects of DBS [59], but unfortunately have lower spatial resolution compared to single or multi-unit recordings [57, 60, 61]. Most notably, LFPs can be recorded using the DBS electrode, thus presenting a unique opportunity for elucidating the effects of DBS while minimizing surgical invasiveness [34–36, 59, 62, 63].

Global field potentials

Global field potentials represent whole brain electrophysiological activity and are thus used to measure spontaneous or evoked responses from large groups of neurons [48, 64, 65]. Global field potentials are most commonly measured via electroencephalogram (EEG) or electrocorticogram (ECoG). EEG electrodes are placed on the scalp and provide signals with high temporal resolution that can be recorded non-invasively. However, these signals are limited by low spatial resolution. ECoG electrodes are placed directly on the surface of the brain and offer improved spatial resolution, but at the cost of a surgically invasive procedure [48]. Global field potentials cannot selectively measure neural activity changes in specific subcortical structures, which limits their applicability as feedback signals for closed-loop DBS.

However, when combined with other neural activity monitoring techniques, such as fMRI and neurochemical monitoring, EEG and ECoG may prove very useful in characterizing the effects of DBS on network dynamics [13].

Neurochemical Monitoring

Neurochemical monitoring is capable of detecting activity from neurons based on the type of neurotransmitter they release, and thus it presents a good alternative for monitoring dynamic changes in brain activity. The specificity of this type of monitoring could lead to improved understanding of stimulation-evoked effects and serve as the basis for closed-loop systems in a wide variety of disorders. The most commonly used neurochemical analysis techniques are microdialysis, amperometry, and voltammetry, which can detect local changes in neurotransmitter concentrations, including dopamine, adenosine, serotonin, and glutamate [20, 21, 66–70].

Microdialysis

Microdialysis is a neurochemical monitoring technique that collects and measures analytes from extracellular fluid via a probe that is permeable to small molecules [71, 72]. Microdialysis provides high specificity, selectivity, and sensitivity to a myriad of neurotransmitters released into the extracellular fluid [42, 72]. However, microdialysis suffers from limited temporal resolution (on the order of minutes to hours), requires off-line analysis of the collected analytes, and can disrupt tissue in the brain region of interest due to the relatively large size of microdialysis probes [73, 74].

Amperometry

Amperometry is an electrochemical technique in which a constant potential, large enough to oxidize or reduce an analyte, is applied to a carbon fiber microelectrode positioned within a brain region of interest. Electroactive analytes are detected by measuring resulting current changes at the recording microelectrode [72, 75]. Non-electroactive analytes are measured by coating the microelectrode with analyte-specific enzymes, which react with the analyte of interest to form electroactive products that can be

measured [76]. Amperometry provides measurements with high temporal resolution but poor selectivity [72]. This is because any molecule oxidized or reduced at the potential of the electrode will cause a change in current. This greatly increases the complexity of chronic in vivo amperometry measurements. Additionally, chronic measurements of non-electroactive analytes require a continuous supply of enzyme to react with the analyte of interest [77]. Thus, the complexity and poor selectivity of chronic in vivo amperometry limits the utility of this technique in the development of real-time closed-loop DBS systems.

Fast scan cyclic voltammetry

Fast-scan cyclic voltammetry (FSCV) is an electrochemical analysis technique used to detect electroactive analytes. A linearly varying potential is applied to an electrode implanted into the brain region of interest [72, 78]. The electrode potential is varied over a voltage range that allows oxidation and reduction of the

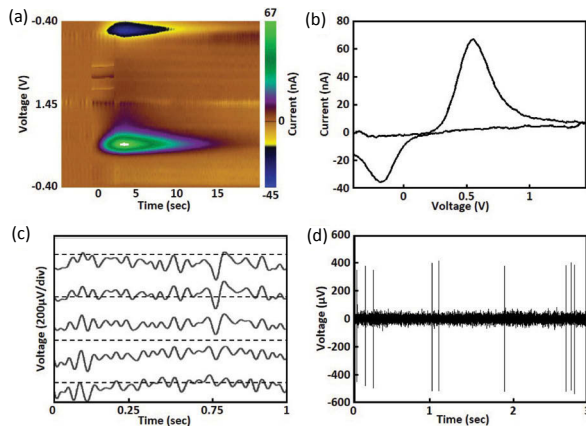


Figure 21.1 Electrochemical and electrophysiologic feedback signals for a closed-loop DBS system. (a) Pseudo-color plot showing a neurochemical recording of stimulation-evoked dopamine release recorded using FSCV at a carbon fiber microelectrode in a swine model of DBS (130 Hz, 0.4 ms, 3.75 V); (b) Cyclic voltammogram for dopamine signal at the dopamine oxidation potential. In (a) and (b) dopamine oxidation is observed at approximately 0.6 V and reduction at -0.2 V. (c) Multi-channel electrocorticogram (ECoG) recording. (d) Single unit recording. Abbreviations: FSCV, fast-scan cyclic voltammetry; DBS, deep brain stimulation.

surrounding electroactive molecules as the evoked currents are measured [72, 79, 80]. The resulting *electric current vs. applied potential* relationship, also known as a voltammogram (Fig. 21.1), serves as a chemical identifier of the target neurotransmitter. In the voltammogram, the magnitude of the oxidation and reduction current peaks are directly related to the concentration of analyte [79, 81]. The subsecond temporal resolution and good chemical selectivity of FSCV have allowed its use for in vivo and intraoperative recordings of dopamine, serotonin, and adenosine concentrations in animals and human patients [20, 79, 80]. In addition, in vivo dopamine measurement via FSCV has been used to establish a proof-of-principle closed loop DBS controller [13].

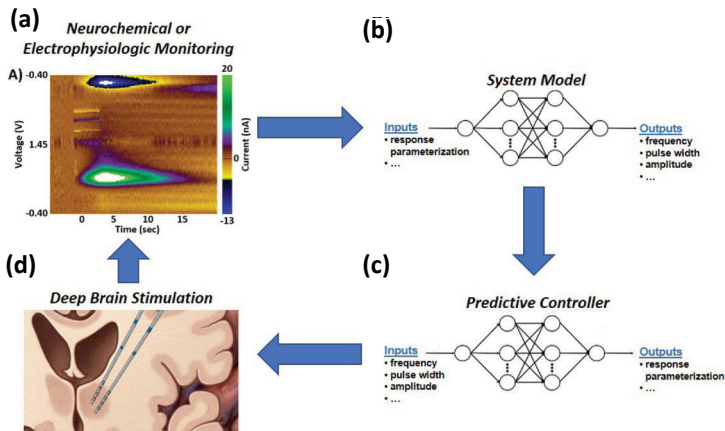


Figure 21.2 An example of a real-time closed-loop DBS system using neurochemical feedback. (a) A pseudo-color plot showing changes in dopamine measured in response to DBS and which can be used as feedback inputs in a closed-loop DBS system; electrophysiologic data are not shown here; (b) Features, referred to as “response parameters,” are then extracted from the recorded neurochemical data. A mathematical model describing the system, represented here by a diagram of an artificial neural network, is then trained to express the relationship between response parameters and stimulation parameters; (c) A predictive controller is constructed by mathematically inverting the relationship modeled in (c); (d) The predictive controller, in conjunction with real-time recordings of neural activity, is used to predict therapeutic DBS parameters used clinically. Abbreviations: FSCV, fast-scan cyclic voltammetry; DBS, deep brain stimulation.

Functional Imaging Techniques

As an adjunct to neurochemical and electrophysiological techniques, functional imaging may be an invaluable tool in the development and validation of closed-loop DBS systems. Unlike conventional neuroimaging techniques, which are used to study brain structure, functional imaging can be used to study brain function and can thus help identify neural circuitry involved in the clinical effects of DBS [10, 41, 82, 83]. Furthermore, functional imaging can be used to identify optimal stimulating and recording targets for closed-loop DBS.

Positron emission tomography and single-photon emission computed tomography

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are nuclear medicine techniques that can be used to explore the effects of DBS through analysis of regional cerebral metabolism and cerebral blood flow [10, 84]. PET detects pairs of gamma rays produced by an electron-positron annihilation event, and reconstructs these data into a 3D image of radiopharmaceutical concentration [85]. This allows the imaging of positron-emitting radiopharmaceuticals, such as fluorine-18 fluorodeoxyglucose, which is used for quantification of cerebral glucose metabolism, an indirect measure of neural activity [84, 86, 87]. In contrast, SPECT imaging detects the emission of gamma photons by radiopharmaceuticals using a gamma camera that rotates around the subject. Similar to PET, these data are reconstructed into a 3D image of radiopharmaceutical concentration [88, 89]. Functional brain imaging uses brain perfusion SPECT with ^{99m}Tc -hexamethylpropyleneamine-oxime as a radiotracer to measure regional cerebral blood flow [10, 84].

Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is a functional imaging technique that measures changes in the inhomogeneity of the magnetic field experienced by hydrogen atoms resulting from changes in blood oxygenation [51, 90, 91]. Due to the coupling of hemodynamics with neural activity, fMRI provides an indirect measure of neural activation. Human and animal fMRI studies have shown that DBS of specific targets evokes consistent patterns

of activation, and have thus provided useful insights into the network effects of DBS [51, 82, 83, 90, 91].

It is important to note, however, that the relationship between the blood oxygen level dependent (BOLD) signal recorded by fMRI and the associated neuronal activity is complex. First, fMRI signals may reflect changes in firing rates and subthreshold activity and do not distinguish between areas of neuronal inhibition and excitation [90, 91]. Second, fMRI signals reflect the activity of multiple neurons and are thus unable to differentiate between large changes of activity in few neurons and small changes generated by many neurons [90, 91]. Despite these issues, functional brain imaging offers the advantage of providing global assessment of synchronous neural activity.

CHARACTERIZATION AND MODELING OF STIMULATION-EVOKED NEURAL ACTIVITY

Development of a closed-loop DBS system will require characterization of the neural response to stimulation across cortical and subcortical networks [58]. To date, such feedback systems have relied on electrophysiological recordings, such as LFPs [34–36]. However, electrophysiological activity alone cannot capture the activity from specific neuronal groups in response to DBS. For this reason, monitoring neurochemical activity may be better suited for modeling the dynamics of stimulation-evoked neural responses.

Recently, Grahn and colleagues described a novel approach to closed-loop DBS that relies on FSCV and artificial neural networks to quantify, and automatically adjust, stimulation parameters as a function of dopamine release in a rodent model of DBS [13]. By combining non-linear regression, computational modeling, and constrained optimization techniques, Grahn and colleagues were able to mathematically parameterize stimulation-evoked dopamine responses associated with DBS. In their study, the inverse dynamics of stimulation-evoked dopaminergic responses were modeled using artificial neural networks [13, 92]. The same neural networks were used to predict stimulation parameters required for sustaining target dopaminergic concentration levels in real-time. Although focused on stimulation of the ascending

dopaminergic fibers in the medial forebrain bundle (MFB) to evoke striatal dopamine release [66], this closed-loop paradigm can be generalized to a variety of analytes, targets, and neurologic disorders.

Monitoring of Stimulation-Evoked Neurochemical Species

The dynamics of stimulation-evoked neurochemical release have been measured for multiple analytes under a comprehensive range of stimulation parameters using FSCV and carbon fiber microelectrodes in anesthetized rats [13, 93–95], pigs [68], and non-human primates [96]. For example, stimulation-evoked dopamine measurements have been obtained by ramping the electrical potential of the carbon fiber microelectrode from a holding value of -0.4 V to a switching potential of 1.5 V at a rate of 400 V/s. The electrical potential was then ramped back to the holding potential to form a triangular waveform, which was repeated every 100 ms [25]. When sufficient potential is applied to the carbon fiber microelectrode, dopamine is oxidized to dopamine-o-quinone, donating two electrons that are detected as current during the positive slope of the triangular waveform. Dopamine-o-quinone is later reduced back to dopamine during the negative slope of the triangular waveform by gaining two electrons and producing an electrical current in the opposite direction. The dopamine concentration (or that of other electroactive analytes) can then be estimated from the measured oxidation and reduction current peaks using pre- and post-operative calibration of each carbon fiber microelectrode via in vitro flow injection analysis [69]. The potentials at which oxidation and reduction of an electroactive analyte occur can be used as a chemical signature to differentiate neurochemical species of interest [72]. Additionally, this approach can be tailored to improve selectivity or sensitivity for different neurochemical species by modifying the FSCV parameters such as the potential waveform, scan rate, holding potential, and switching potential.

Computational Modeling of Neurochemical Responses

As noted earlier, implementation of neurochemically driven closed-loop DBS control strategies requires mathematical modeling of

the relationship between electrical stimulation and neural responses. In the proof-of-principle closed-loop DBS controller developed by Grahn and colleagues [13], the features required for feedback control were extracted by fitting the stimulation-evoked dopamine response to individual stimulation parameters with a combination of mathematical models, such as polynomials and exponentials [13]. Machine learning techniques, such as artificial neural networks and fuzzy logic [97], can then be used to model the relationship between stimulation parameters and features extracted from stimulation-evoked neurochemical (and/or electrophysiological responses) [13, 92, 98].

STIMULATION PREDICTION

Like the learning brain, artificial neural networks trained on generalized input-output data can adapt to changing environments based on experience. As such, they are ideal for developing stimulation predictors based on mathematical representations of stimulation-evoked neurochemical responses. For optimal therapeutic benefit, a closed-loop controller must determine, in real-time, the stimulation parameters that will sustain a target therapeutic neural response. To achieve this, the DBS controller must be able to anticipate or predict the stimulation required to sustain therapeutic levels of neural activity. In this section we use the example of predictions based on neurochemical feedback.

The closed-loop system proposed by Grahn and colleagues suggests that mathematical models can be used to describe the relationships between stimulation-evoked extracellular neurotransmitter responses and DBS parameters. Using stimulation-evoked responses from the brains of anesthetized rodents, they were able to characterize how each brain responded to electrical stimulation. This type of data represents the input from which a mathematical model could be derived, and through a process of machine learning, make the first step toward predicting the stimulation parameters required to achieve a patient-specific therapeutic response.

The next step involves inverting this relationship, also known as transfer function, so that the predictive stimulation controller can determine the parameters required to evoke a predetermined or “target” neural response. Artificial neural networks can learn

almost any non-linear relationship between a set of inputs and a set of outputs, and thus, networks that have been trained on stimulation-evoked neurochemical responses can easily adapt to the inverse relationship between target neural responses and the stimulation parameters needed to achieve them. In a feedforward configuration, artificial neural networks can predict the stimulation parameters required for achieving static target neurotransmitter concentration levels. When the current neurochemical state of the target region is fed back into the neural network inputs, an artificial neural network can adapt the stimulation parameters in such a way as to sustain predetermined optimal neurotransmitter concentration levels despite a changing environment. That is, based on experience, a dynamic artificial neural network can adjust its internal representation of the relationship between the inputs (e.g., target and actual neurochemical responses) and the outputs (e.g., stimulation duration, frequency, amplitude, pulse width, etc.) within the context of the brain's dynamic environment.

The ultimate goal is that in a human patient, the predicted stimulation parameters could be further fine-tuned to optimize a patient-specific therapeutic response. They would do so by combining artificial neural networks and fuzzy-logic approaches that can be dynamically adjusted relative to the response of an individual patient [99].

ADDITIONAL CONSIDERATIONS

Frequent adjustment of stimulation settings has been shown to improve the efficacy of DBS therapy [34], which highlights the brain's dynamic nature and emphasizes why a smart, automated system capable of dynamically adjusting stimulation parameters is critical for improving the efficacy of DBS therapy. By taking advantage of mathematical models, smart closed-loop DBS devices could use deterministic approaches to replace the trial-and-error process currently used in clinical programming. Closed-loop devices would not only assist clinical teams in achieving optimal therapeutic outcomes, but would also minimize the number of clinical interventions.

However, the performance of mathematical modeling approaches is highly dependent upon the uniqueness, quantity,

and quality of the data features, the amount of data used to create the models to make predictions, as well as the specifics of the experimental paradigm [97]. Thus, special attention must be placed on the use of appropriate neural activity detection paradigms, as well as on the selected modeling and training strategies so as to avoid over-fitting the training data, extracting too many features, or using too few trials [97].

Additionally, selected neurotransmitters and recording locations should be well characterized for each disorder in order to create an optimal feedback system for therapeutic DBS. While region-specific DBS mechanisms have been investigated using electrophysiology and electrochemistry, the complex, dense wiring of the brain makes understanding neuronal communication beyond a few synapses extremely challenging. Thus, the insights into the network effects of DBS provided by fMRI may be crucial for determining appropriate placement of stimulation and recording electrodes, as well as for elucidating the effects of therapeutic and non-therapeutic stimulation.

Another important technical barrier has been the lack of a suitable chronic recording electrode for FSCV. It is worth commenting on the sensitivity issues associated with use of carbon fiber microelectrodes for long-term or “chronic” recording. In particular, the surface of a carbon fiber microelectrode electrode adsorbs dopamine between scans, which causes both the holding potential and the inter-scan interval to affect the intensity of the recorded electrical current signals [72]. Additionally, electrode sensitivity decreases following electrode implantation into brain tissue [72, 100]. Furthermore, the unbalanced nature of the FSCV waveforms required for measuring electroactive neurotransmitters produces fouling of the carbon fiber microelectrodes. These sensitivity issues inherent in carbon fiber microelectrodes as well as the immune response to the inserted electrode should be considered when designing new neurochemical detection paradigms for chronic, real-time recording of neurotransmitter concentrations. Efforts are underway to develop electrochemical-sensing techniques capable of extending electrode longevity by renewing the electrochemically active surface following adsorption of chemical species [101]. It has been reported, for example, that diamond coating may prolong the life of recording electrodes [102].

Lambert and Blaha concluded that burst-like stimulation allows for increased dopamine release compared to current clinical stimulation techniques that rely on DBS that is always ON (C. Blaha, personal communication). Additionally, other research suggests that DBS with ON and OFF periods can increase implanted stimulator battery life [35, 103]. Thus, a closed-loop DBS controller could monitor dynamic changes in brain activity to determine when to deliver stimulation and when to stop stimulation, allowing for more effective symptom control and increased battery life.

Before automated adjustment of stimulation parameters can be clinically implemented, a key clinical question needs to be addressed. Specifically, what is the relationship between neurotransmitter levels and symptoms of neurologic disease? For example, while evidence suggests that dopamine depletion plays a role in the symptoms of PD, the exact changes in neurochemical concentrations that occur with symptom exacerbation and amelioration remain unknown. Multiple neurotransmitters may play a role, and it is unclear which ones are primarily responsible for the therapeutic effects observed [104]. Future work should be directed toward establishing correlations between neurotransmitter release and the therapeutic benefit of DBS across different neurologic conditions. Additionally, identifying target locations for optimal monitoring of neurochemical and electrophysiologic activity associated with various neurologic conditions and the therapeutic effect of DBS may require the use of functional imaging techniques. As these and other techniques are being considered for developing closed-loop DBS systems, they are all currently being used to help characterize the relationship between stimulation and its clinical effect.

SUMMARY

Conventional open-loop DBS systems have been successful at achieving therapeutic outcomes in patients with certain neurologic and psychiatric disorders. However, limitations in existing technology make ensuring optimal benefits a difficult and expensive endeavor. By automatically responding to the dynamic, real-time

changes from recordings of neural activity (electrophysiological or neurochemical), closed-loop systems address many issues hindering the performance of the existing clinical DBS paradigm. Additionally, functional neuroimaging may play an important role in the development and validation of closed loop DBS systems by providing insight into optimal stimulation and recording targets at both the local and network level [82–84]. Finally, the versatility and adaptability of closed-loop systems will allow tailoring of DBS therapy to individual patients and symptoms which will likely improve clinical outcomes, reduce the length and frequency of patient visits, and lower overall health care costs.

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Chapter 22

Molecular and Cellular Neuromodulation for Central Nervous System Injury and Regeneration

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INTRODUCTION

The central nervous system (CNS) is an intricately evolved organ that requires the precise interplay between neurons, glia and support cells to govern peripheral functions and complex, higher-order central cognition. The brain itself is comprised of roughly 100 billion neurons, each averaging roughly a thousand synaptic connections that participate in a finely choreographed orchestration of intrinsic and extrinsic cellular factors to provide the fundamental framework for developmental wiring and continued synaptic maintenance. Disease or traumatic injury may sever these connections, resulting in loss of function and vastly amplified rates of morbidity and mortality.

Promoting CNS regeneration and functional recovery of neural circuitry after injury or disease poses unique challenges

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when compared to the natural instigation and growth of neural connectivity during embryonic development. These challenges include diminished rates of intrinsic axon outgrowth capacity, major differences in the scale required for re-connection, and a largely hostile injury microenvironment. To date, no single therapeutic intervention has produced full restoration after injury in the mammalian CNS, although many molecular, cellular, and rehabilitative treatments have been evaluated in both animal and human trials. Pioneering advances in molecular and cellular neurosurgery hold promise in offering safe, highly effective, targeted interventions for positively controlling neural responses to disease and injury. Furthermore, directed neuromodulation may offer insights into mechanisms for enhancing natural human cognitive performance and abilities. This chapter will review both ineffective and promising biological therapies under investigation that are aimed at restoring lost connections due to traumatic injury or neurologic disease and will close with a discussion on where these areas of investigation may take us in the years to come.

INTRODUCTION TO NEURAL REGENERATIVE INTERVENTIONS

The adult mammalian central nervous system (CNS) is a tightly structured organ that demands the successful interaction among a vast collection of cell types. Chemically and electrically active neurons, homeostasis-modulating glia, progenitor cells, peripherally derived cells, and vascular elements all work in close juxtaposition to allow for complex neural activity. Traumatic injury or neurodegeneration that damages one or more of these components may lead to major lapses in function, and normal tissue architecture and function are largely unable to be restored once an individual has progressed to maturity and past critical periods of development. When an insult occurs, the various CNS cell types in addition to infiltrating immune and stromal cells from the periphery undergo dramatic changes in cell morphology, motility, and purpose in an effort to halt the injury propagation and maintain or restore a degree of homeostasis and normal performance.

Full restoration of the adult CNS faces numerous challenges. Local responses to CNS injury are heterogeneous and often include

hemorrhage, inflammation, excitotoxicity, apoptosis, demyelination, edema and cyst formation, production of free radicals, loss of lipid and membrane integrity, and cellular and collagenous scar formation (Fig. 22.1). Many of these responses may provide early protective benefits, but ultimately impair complete regeneration. For example, early cytokine and chemokine responses by peripheral immune cells and microglia, in addition to physical barriers from fibroblasts and astrocytes, may prove to be advantageous in restricting the primary injury radius [1, 2]. However, these responses, meant to govern spread of the injury, may also later serve to impede migration of progenitor cell populations into the lesion site, as well as limit vascular flow for the clearance of cellular debris and delivery of exogenous therapeutic agents [3].

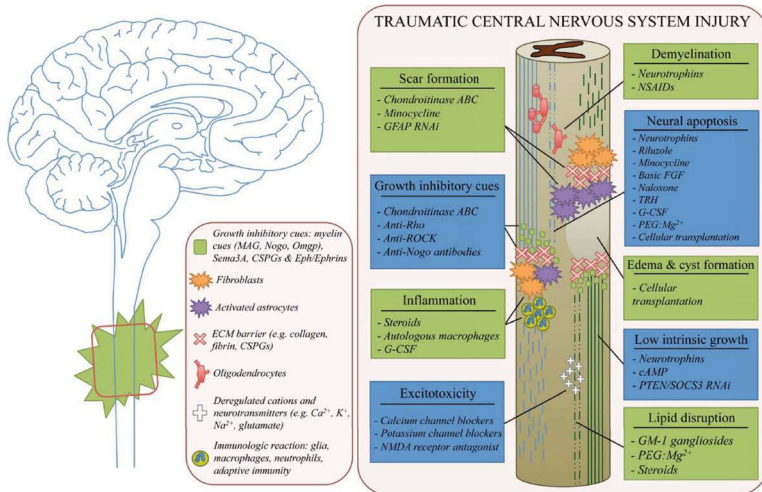


Figure 22.1 Pathophysiologic mechanisms of traumatic spinal cord injury and therapeutic interventions aimed to manage them. These mechanisms result in cellular and ECM remodeling, cell death, and failure of axons to reestablish connections leading to permanent loss of function.

In addition to robust immunologic and cell barrier reactions, several other hurdles exist for successful regeneration. Damaged and apoptotic oligodendrocytes, which already disrupt function through loss of their axon-insulating myelin sheath, release solubilized myelin breakdown products, such as Nogo, myelin-associated glycoprotein (MAG) and oligodendrocyte-myelin

glycoprotein (OMgp), which may act as potent inhibitors to axon regenerative growth [4–12] (Fig. 22.2). Chondroitin sulfate proteoglycans (CSPGs) [13, 14], Semaphorin 3A (Sema 3A) [15–17], Ephrin B2 and B3 [18, 19], and Eph 4A [20] are additional factors found within the local injury site that may further an axon growth-impermissive environment (Fig. 22.2). Moreover, adult axons themselves have a reduced intrinsic capacity for regenerative growth and sprouting, and their synaptic targets often atrophy and become reorganized over time [14]. Thus, successful interventions promoting CNS regeneration and restoration of function will likely need to be multifaceted and target at least several of these barriers, all while minimizing systemic adverse effects.

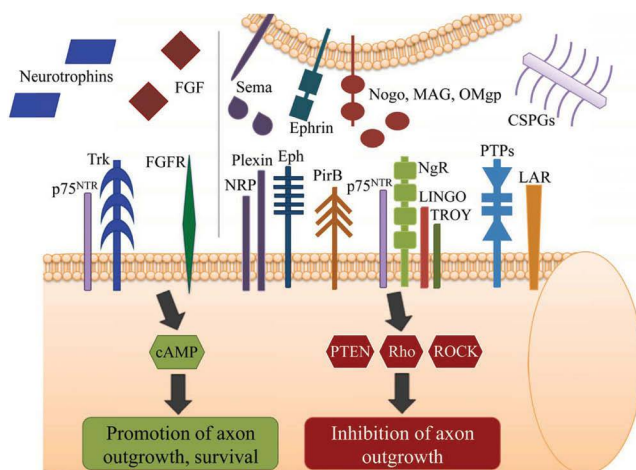


Figure 22.2 Ligands and receptor complexes involved in regulating intracellular signaling cascades that promote or inhibit axon growth and survival. Both developing and injured axons express a combination of receptors utilized for proper guidance or resulting in limited outgrowth capacity, respectively (bottom). Ligands for these receptors may be solubilized or expressed on the surface by glial cells (top). Signaling pathways initiated by ligand: receptor binding can lead to the promotion of cellular survival or stimulation of axon elongation, often through modulating cAMP in some fashion. Conversely, inhibitory signals may lead to disruption of axon outgrowth through modulating phosphatases such as PTEN or GTPase family members and their effectors, Rho and ROCK, respectively.

Traumatic injury and neurodegenerative disease in the CNS are often heterogeneous in nature and manifest with multifarious signs and symptoms, making it challenging to establish robust animal models and assess reliable outcomes in clinical trials. However, spinal cord injury, while equally complex, lends itself to determining discrete recovery of motor and sensory limb abilities, as well as bowel, bladder, and sexual function. For the purposes of comparing different modalities of molecular and cellular interventions for neuromodulation of CNS regeneration, this chapter will focus primarily on models and trials that evaluated spinal cord injury (SCI) therapeutics.

Many of the therapies for SCI that prove efficacious at limiting injury size, preventing cellular apoptosis or restoring function may also prove useful for managing injury and neurodegenerative disease in supra and infratentorial regions. In addition, the development of molecular and cellular interventions, particularly those that are amenable for stereotactic targeting to discrete regions of the CNS, may prove invaluable in improving our understanding of neurobiology and for the efficacious management of complex psychiatric conditions, epileptiform disorders, cancerous lesions and even enhancing current limits of human cognition.

HISTORICAL NEURAL REGENERATION PERSPECTIVE

“It is to be noted that if a nerve is cut lengthwise, it is possible to heal it by the following treatment. Steep earthworms in oil and place the oil, warmed over the fire, upon the wound three or four times with no other medications. If it is cut obliquely, it will not heal well with the foregoing treatment, and if it is completely cut obliquely, it will scarcely consolidate at all.” That medical recipe was the prevailing surgical concept for the management of injured “nerves” in the late twelfth century, founded on texts by Roger of Salerno [21]. It is an approach that demonstrates the poor appreciation of basic nervous system physiology at the time. It also illustrates that while human biomedical research has advanced tremendously, as has our understanding of the mechanisms of and barriers to recovery from neural injury,

our ability to directly modulate neural connections and restore function has not progressed much since the twelfth century.

The first published evidence of spontaneous peripheral neural regeneration came in the eighteenth century, from the English anatomist, William Cruikshank, who observed injured canine vagal nerves over time in an attempt to understand cardiovascular innervation physiology [22]. He serendipitously found a “substance uniting the cut ends” of the vagus nerve several days after they were severed, which he later determined was regrown peripheral nerve [22]. The Roman physician Galen had made the observation that nerves controlled sensation and motion several centuries earlier, although a modern understanding of neural physiology was not attained until the late nineteenth century through the works of Golgi and Ramon y Cajal [23, 24].

Modern science and medicine has greatly advanced our understanding of the pathophysiology underlying failure of the nervous system, particularly the CNS, to regenerate after injury. However, successful interventions remain elusive, and our current strategies are not significantly more advanced than that of Roger of Salerno’s time. Electrical neuromodulation became popularized in the early 1960s with the first report of deep brain stimulation followed closely by the first reported case of spinal cord stimulation [25, 26]. Developing interventions for modulating the CNS provides opportunities to restore function, as for example with cochlear implants or the transplantation of motor neurons in patients with amyotrophic lateral sclerosis (ALS), to manage chronic conditions like pain, and for the control of symptoms for essential tremor or Parkinson’s disease. The following text outlines contemporary therapeutics at various phases of translational development into clinical practice for modulating neural function, with special attention to those for restoring neural function after injury or disease.

NEURAL PROTECTION AND AXON OUTGROWTH STIMULATION

Growth Factors

Traditionally, therapies to promote mammalian CNS regeneration have been designed to address a single one of the numerous

individual inhibitory roadblocks to natural recovery. Many of the agents evaluated to regenerate the spinal cord have come from investigations into how the nervous system undergoes embryonic development, and in particular the secreted factors that promote axon outgrowth and chemoattractive guidance. Some of the most promising interventions over the last few decades have precipitated from the Nobel Prize winning work of Stanley Cohen and Rita Levi-Montalcini, in addition to seminal work from Viktor Hamburger of the effects on motor neuron columns from manipulation of developing chick limbs [27]. The discovery that a peripherally derived factor was instrumental in both spinal motor neuron guidance and survival paved the way for neuroembryonic investigations into the intertwined role of neuronal cell populations and their innervated cells and tissues. The pioneering discovery of nerve growth factor (NGF) in the 1950s, which led to the Nobel Prize in Physiology or Medicine in 1986, and of brain-derived neurotrophic factor (BDNF) by Hans Thoenen and colleagues in 1982, has proved instrumental in our understanding of neuronal survival, signaling and guidance [28–30]. Several additional neurotrophins that display varying degrees of tropism for certain subclasses of neuronal cell populations have been well characterized.

Neurotrophins, which play important physiologic roles in neuronal survival, axon outgrowth, and synaptic plasticity and maintenance throughout development and adulthood, make attractive therapeutic candidates for promoting regeneration after injury (Fig. 22.2). Early rodent work with the infusion of NGF, neurotrophin-3 (NT-3) or particularly BDNF demonstrated great promise as potent neuroprotective and potentially regenerative agents to injured spinal cords [31–34] (Fig. 22.3). Treatment with BDNF in animal models was found to not only improve neuronal survival and axon outgrowth but also promote remyelination from oligodendrocytes, stimulate axon sprouting, and even to possess some anti-oxidant potential for decreasing nitric oxide production [35]. Delivery of exogenous neurotrophins was found to promote axonal outgrowth of discrete neuronal populations, including NGF on coeruleospinal axons [36, 37], NT3 on corticospinal (CST) axons [38], GDNF on dorsal column sensory and motor axons in addition to promoting remyelination [3, 39], and BDNF on raphespinal, reticulospinal, vestibulospinal,

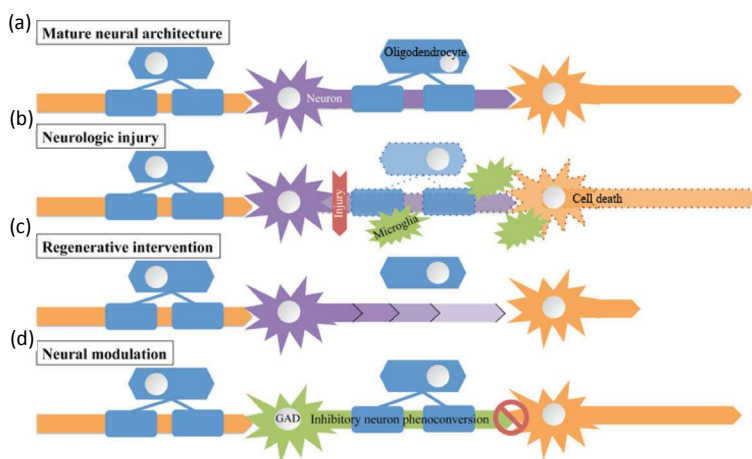


Figure 22.3 Modulating the mature nervous system after injury to restore damaged connections or to modulate neuronal activity. Normal mature neural architecture (a) can be disrupted after injury or disease leading to microglial activation, axon degradation, and oligodendrocyte and neural cell death (b). Interventions aimed at restoring neuronal function have largely targeted the promotion of axon outgrowth or cell survival (c). Alternatively, normal neuronal function may also be disrupted by over-activity or reduced regulation of activity, as in the case of epilepsy. For these instances, neural activity may be modulated gene expression, GAD in this instance, to phenoconvert neuronal subpopulations from excitatory to inhibitory classes (d).

and rubrospinal tracts. It also partially restored forelimb function in a rat cervical hemisection injury model [40–43]. Combination treatments saw even greater functional outcomes. For example, BDNF and NT3 administration improved hindlimb and bladder function after thoracic contusion injury [44]. Conversely, human clinical trials with systemic delivery of NGF and BDNF showed little efficacy [45–47]. Current maxims suggest that these trials were unsuccessful for several reasons, including inability to penetrate the blood–brain barrier and spinal cord lesion site, costly side-effect profiles, insufficient trafficking of the neurotrophin tyrosine kinase cognate receptors to distal regions of severed axons, and failure to promote axon outgrowth over local inhibitory factors such as myelin-associated glycoprotein (MAG) [35, 48, 49]. More recent studies indicate that neurotrophin

administered locally at either the lesion site or neuronal cell bodies may alleviate some of the adverse effects and augment functional outcomes [3, 50].

Additional growth factors and molecular agents to positively influence neuronal survival and function have also shown promise in pre-clinical animal trials. Basic fibroblast growth factor (FGF) demonstrated early potential in promoting survival in preganglionic sympathetic motor neurons and in partially rescuing respiratory function in a rat contusion thoracic injury [51]. However, a non-controlled phase I/II trial in chronic SCI human subjects who received acidified FGF in combination with local administration of fibrin glue showed meager improvements in American Spinal Injury Association (ASIA) motor and sensory scores [52, 53].

Anti-Neuronal Apoptosis

The development of agents that halt neuronal cell death would be exceptionally valuable for the management of CNS damage from stroke, traumatic injury, or from neurodegenerative disorders, such as ALS and Huntington's disease. Such agents also might potentially augment quantities of neural progenitor cells to aid in memory preservation and enhancement. Substantial libraries of pharmaceutical agents have been investigated for their ability to promote neuronal survival after CNS injury, particularly agents that have already received FDA approval for other disorders, which would allow for rapid clinical translation. Minocycline, a tetracycline antibiotic traditionally prescribed for acne, was first noted to prevent hippocampal pyramidal cell death in a gerbil forebrain ischemia model [54] and was further shown not only to promote neuronal survival but also to decrease microglial activation and restore a degree of hindlimb function in rodent SCI models [55–57]. Conversely, later reports failed to reproduce the rodent functional behavioral recovery from minocycline administration, and one study even indicated that prolonged treatment impaired motor neuron survival [58–60]. A placebo-controlled, randomized phase II trial of systemic minocycline administration in acute SCI showed no statistical benefits, but ASIA scores trended towards significance in cervical injury patients [61].

Granulocyte colony-stimulating factor (G-CSF), which has traditionally been used for the management of neutropenia and the promotion of peripherally derived bone marrow stem cell mobilization into systemic circulation, has also shown promise in suppressing neuronal and glial apoptosis and positively modulating the lesion site by decreasing inflammation and stimulating angiogenesis after injury stabilization in mice [62–64]. A small, non-randomized phase I/IIa clinical trial evaluating five-day systemic treatment with G-CSF demonstrated improvements in light touch and pin prick scores within a few days, and at least half of the treatment group experienced a grade increase in ASIA grade [65]. One year follow-up evaluation of patients who received G-CSF found sustained improvement in motor scoring over control subjects [66].

Axon Outgrowth Dynamics

Myelin-based inhibitory factors

Directly modulating function and activity of inhibitory axon outgrowth factors released after SCI has been well investigated over the past few decades. Factors solubilized after oligodendrocyte and myelin damage, including Nogo, MAG and OMgp, are thought to be significant contributors to the inhibition of axon outgrowth after injury. Efforts to use antibodies targeting individual myelin components or their cognate Ng receptors have shown promise in enhancing CST axon sprouting, but have led to mixed functional benefits in rodents [10, 67–71]. This varied efficacy may result from the presence of multiple myelin factors at the spinal cord injury site in addition to subsequent identification of a second major receptor for myelin-based cues [72, 73]. A cervical unilateral lesion in adult non-human primates followed by anti-Nogo antibody treatment enhanced CST axon sprouting and manual dexterity [74, 75]. However, there were concerns about the validity of conclusions made in the initial study [76, 77]. A phase I clinical trial delivering intrathecal Anti-Nogo antibody (ATI355) to test for safety, pharmacokinetics, tolerability and feasibility was completed in 2011 (NCT00406016); results have yet to be made available, but a phase II trial is underway [78].

Second messenger pathways

Many axon outgrowth inhibitory factors, including the myelin-based cues, negatively regulate growth mechanisms and axonal cytoskeleton dynamics through activity of the GTPase Rho and the downstream Rho kinase ROCK, which regulate cytoskeletal dynamics to modulate cellular and axonal motility. Blockade of Rho function using the bacterial toxin C3-ADP-ribosyltransferase stimulated regenerative axon growth and functional hindlimb recovery in a mouse dorsal hemisection model [79], but failed to promote CST axon outgrowth in a rat dorsal hemisection injury [80]. Negatively targeting the Rho downstream effector p160ROCK using Y-27632 stimulated axon outgrowth on myelin-substrates in vitro, promoted CST fiber regrowth in vivo and accelerated hindlimb behavioral recovery [80]. Concern over safety and efficacy of systemic delivery of a Rho antagonist led to the development of a cell-permeable version (Cethrin, BA-210) delivered locally in combination with fibrin during surgical spinal decompression. When applied to the dura within seven days of SCI in a small phase I/IIa clinical trial, patients with complete ASIA grade A scores demonstrated that at optimal dosage 66% of them converted from ASIA A to ASIA C or D, with no major adverse effects across any of the treatments [81].

Small molecule inhibitors of ROCK showed early promise in rodent models, but have been approached with caution due to potential teratogenicity and the possibility of stimulating inhibitory CSPG secretion from astrocytes [82–85]. Non-steroidal anti-inflammatory drugs (NSAIDs), which are traditionally used to inhibit cyclooxygenase (COX) activity for analgesia and to manage inflammation, have also been discovered to suppress intracellular RhoA activity [86]. Antagonizing RhoA with ibuprofen or indomethacin, but not the COX-2 specific NSAID naproxen, demonstrated a multifaceted capacity for promoting axon sprouting, regenerative axon growth, remyelination and improved motor recovery, in addition to suppressing neural apoptosis [86–88]. A meta-analysis by Watzlawick and colleagues [89] compiled all spinal cord injury pre-clinical trials that evaluated motor recovery in animals with hemisection, contusion or complete transection after treatment with a Rho/ROCK inhibitor [89]. They determined that blockade of Rho or ROCK led to a 15% improvement in functional motor recovery [89].

Targeting additional cytoplasmic second messengers that are important for successful nerve growth and guidance during development may prove to be essential for stimulating the intrinsic outgrowth capacity of adult neurons after injury. Cyclic adenosine monophosphate (cAMP) promotes neuronal survival, bidirectional axon guidance, and stimulates nerve growth by neurotrophins and other guidance factors in developing neurons [90–94]. In addition, they serve an important role in memory enhancement and as a potential therapy for neurodegenerative diseases [95–97]. Furthermore, intracellular cAMP levels are elevated in embryonic neurons and rapidly decrease postnatally in rats, a decrease which strongly correlates with the onset of suppressed neuronal growth by myelin-based factors [98].

A priming lesion of peripheral dorsal root ganglion (DRG) axons has been shown to enhance the regenerative growth capacity of subsequently injured central DRG axons, a mechanism by which cAMP is both sufficient and necessary [99]. Elevation of cAMP, through the use of synthetic analogues or by disrupting conversion to an inactive form by phosphodiesterase inhibitors demonstrated robust ability to stimulate endogenous regenerative axonal outgrowth leading to functional motor recovery in animal models [100–102]. Combination treatments with cAMP and cellular transplantation or neurotrophins have proven complimentary in promoting mammalian CNS regeneration [103, 104]. Therapies designed to enhance cAMP activity at the neuronal cell body have increased regenerative growth of spinal motor axons populations in a complete spinal transection model, but paradoxically led to a reduction in functional recovery [105], highlighting the complexity of mammalian spinal cord regenerative efforts.

Intrinsic growth capacity

Efforts to neutralize inhibitory factors in the CNS lesion environment have resulted in only modest gains in regenerative axonal outgrowth. This poor response suggests that the intrinsically ineffectual growth capacity of injured adult neurons may also play a strong role in the lack of functional regeneration. Targeting the expression of genes involved in the tight regulation of preventing cellular overgrowth after embryonic and early development might reconstruct a neuronal RNA transcriptome and

proteasome comparable to that exhibited during developmental axon guidance. Deletion of phosphatase and tensin homolog (PTEN), a negative modulator of the mammalian target of the rapamycin (mTOR) pathway and an important regulator of cellular growth and migration [106], stimulated axon outgrowth from crushed retinal ganglion cells (RGCs) [107]. Additionally, negative regulation of the suppressor of cytokine signaling 3 (SOCS3) and the JAK/STAT pathway similarly promotes regenerative outgrowth in both peripheral and RGCs [108–110]. However, modulating PTEN or SOCS3 genes individually led to stalled axonal growth by 1–2 weeks after crush injury. Conversely, combined deletion of PTEN and SOCS3 in RGCs results in synergistic, prolonged axonal outgrowth [111]. The use of short hairpin RNA to suppress PTEN expression similarly promoted regenerative growth of corticospinal tract axons in a mouse SCI model [112]. The continued development of targeted genetic and RNA expression therapies may permit faster translational progress, allow flexibility with combinatorial interventions, and create an improved safety and regulation profile (Fig. 22.4).

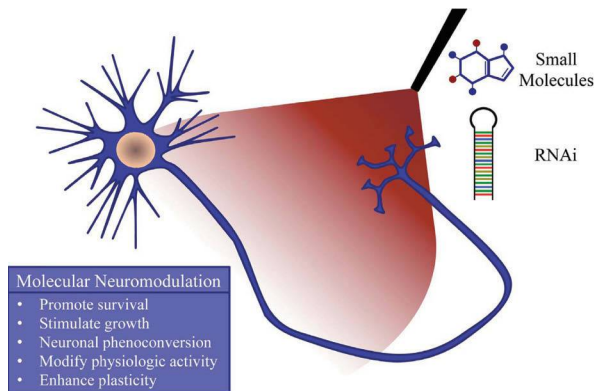


Figure 22.4 Directed therapeutic targeting to discrete neuronal or glial subpopulations to modulate CNS function. Molecular inhibitors or RNA expression modulating agents targeted to desired regions or subtypes of neurons might maximize interventional strategies while minimizing adverse events. This might conceivably be achieved through local stereotactic administration (shown by a black micropipette tip delivering therapeutic factors using a gradient, represented in red) or systemic delivery with agents packaged in vectors with specific tropisms.

RNA Interference and Gene Therapy

Genetic manipulation to regulate expression of various proteins, including neurotrophins, insulin-like growth factor-1, growth-associated protein GAP-43, VEGF, and Kruppel-like factors have been investigated as a means of promoting regeneration through direct gene therapy delivery of viral-vectors [113, 114]. Lentiviral delivery vectors are particularly advantageous because of their ability to transduce both dividing and non-dividing cells such as neurons. In addition, certain viral molecules demonstrate tropisms for specific subclasses of neurons, allowing not only specific stereotactic delivery but also cellular targeting.

The biological process of RNA interference (RNAi) is a powerful approach for silencing gene activity *in vivo* using chemically synthesized, small interfering RNA (siRNA) and vector-based, short hairpin RNA (shRNA) or microRNA systems. Similar to other therapeutic interventions, RNAi suffers from complications, including problems in the efficient delivery and stability of siRNA molecules, off-target activation of toll-like receptors and interferon immune pathways, and complications with viral and non-viral vector delivery systems.

However, despite these issues, RNAi has shown great potential as a novel strategy for molecular neuromodulation, including regeneration [115]. Negatively regulating expression of RhoA and glial fibrillary acidic protein (GFAP) using siRNA resulted in improved serotonergic axon growth and urinary dysfunction, respectively in rats [116, 117]. Furthermore, lentiviral-based shRNA targeting LINGO-1 (LRR and Ig domain-containing Nogo receptor interacting protein), a transmembrane protein involved in the NgR1/p75^{NTR} receptor complex and negative regulator of nerve growth, delivered by a gel polyol promoted rat functional recovery in motor testing after complete thoracic transection in rats [118].

Interestingly, both targeted gene therapy and RNAi may additionally prove valuable in the management of psychiatric disorders, neurodegenerative conditions, or the enhancement of human neurologic function. The successful targeted conversion of excitatory glutamatergic neurons to inhibitory GABAergic neurons in the subthalamic nucleus using the glutamic acid decarboxylase (GAD) gene, which catalyzes production of

GABA, alleviated the parkinsonian behavioral phenotype in rats [119] (Fig. 22.3). Importantly, an early phase I trial of RNAi using systemic nanoparticle-encapsulated siRNA delivery for solid tumor targeting resulted in specific gene and protein knockdown that will surely pave the way for future RNAi trials aimed at CNS injuries [120] with implications for multiple neurodegenerative and traumatic disorders [121].

Lipid and Membrane Integrity

Gangliosides

Gangliosides are naturally occurring lipid compounds in plasma membranes and in specific CNS cell membranes that are involved in cell-to-cell communication and cellular recognition [122]. Investigations over thirty years ago suggested that gangliosides might stimulate axonal sprouting in vitro [123]. Pre-clinical animal trials determined that gangliosides, and in particular GM-1, might convey neural protective effects and promote lasting regenerative outgrowth [122]. The discrete regenerative mechanisms of ganglioside treatment remain uncertain, but hypothesized mechanisms include the prevention of excitotoxicity, promotion of cell survival, and potentiation of axonal sprouting and neurotrophin activity [124, 125]. There is concern that GM-1 treatment may increase the risk for Guillain-Barre syndrome [126], although the connection remains speculative.

A small preliminary phase I clinical trial demonstrated promise for GM-1 treatment [127], but a subsequent large randomized, double-blind study was largely inconclusive in demonstrating a marked functional benefit, with the high GM-1 dose actually increasing mortality [124]. A Cochrane review conducted in 2005 evaluated the two clinical trials employing GM-1 as a therapeutic option for spinal cord injury patients and found insufficient evidence to warrant its use in acute cases [128].

Polymers

The discovery that membrane damage and oxidative stress may play vital roles in the pathophysiology of spinal cord injury have prompted investigations into agents that may attenuate these negative processes. Polyethylene glycol (PEG), a hydrophilic

polymer of ethylene oxide, has been shown to reduce membrane permeability in vitro, to suppress reactive oxygen species (ROS) and lipid peroxidation (LPO), and even to restore compound action potentials in crushed guinea pig spinal axons [129, 130]. However, it seems that the reduced ROS and LPO is a direct mechanism of restoring membrane integrity, rather than a function of the PEG scavenging free radicals or directly regulating superoxide activity [130]. More recently, PEG formulations with additional molecules have been investigated, including combination trials with magnesium chloride. Magnesium chloride may convey its own neuroprotective effects but it results in severe adverse cardiovascular effects when delivered systemically and thus must be provided by controlled, local administration. Pre-clinical trials using a PEG:magnesium chloride formulation in rat thoracic contusion and cervical hemisection models showed enhanced neural protection over methylprednisolone, the longstanding gold standard treatment for SCI and certain neurologic traumas, and demonstrated decreased propagation of secondary injury and increased behavioral recovery [131, 132].

Glucocorticoids

Treatment with glucocorticoids, mainly methylprednisolone sodium succinate (MPSS), has served as the clinical gold standard for acute SCI over the past few decades, but varied results and adverse effect profiles have tempered its use clinically [133]. Rapid administration of MPSS after injury suppresses peroxidation of plasma membrane lipids, regulates Ca^{2+} homeostasis, improves $(\text{Na}^+ + \text{K}^+)\text{-ATPase}$ activity, enhances impulse conduction, and dampens the early inflammatory response [134–136]. The most significant benefits in human clinical trials were observed when MPSS was delivered within 3 to 8 hours of insult and maintained for 48 hours in incomplete injuries [137–141]. Treating patients with MPSS after 8 hours resulted in decreased motor recovery compared to placebo cohorts [137]. Patients receiving MPSS were noted to have significant adverse effects including increased pulmonary distress and infection rates [142, 143]. Furthermore, investigations into trial designs and statistical conclusions suggest that clinical benefits may be unremarkable [144–146]. The American Association of Neurological Surgeons and Congress

of Neurological Surgeons released a statement in 2013 that the use of glucocorticoids for acute SCI is contraindicated [146].

Non-glucocorticoids

Treatment with the non-glucocorticoid steroid 21-aminosteroid tirilazad mesylate, formerly known as U74006F, was developed to inhibit the peroxidation of neuronal membranes and showed early promise preserving hindlimb function in a rat compression model when delivered rapidly after injury [147]. A phase III clinical trial administering a tirilazad bolus infusion every six hours over the course of 48 hours saw benefits comparable to methylprednisolone over the first 24 hours effects which remained persistent at one-year follow-up [139, 140]. However, the authors noted that the tirilazad dose may have been insufficient, and that it was administered to the patients with the most severe injuries [140].

Opioid Antagonism

Many additional neuroprotective therapies have been found to have inconclusive or insignificant benefits. Naloxone, an opioid antagonist that blocks the neurotoxic effects of the endogenous opioid dynorphin A, showed promise as a therapeutic SCI patients, but lost momentum when it was linked with increased post-traumatic pain and in a larger clinical trial failed to show prolonged functional benefit [137, 138]. Thyrotropin-release hormone (TRH) is found to occur naturally in axon terminals that are in close juxtaposition with motor neurons [148] and may act as a partial opioid antagonist that spares analgesic function while suppressing neuronal excitotoxicity [149, 150]. Studies found that it was superior in restoring feline motor function when compared to naloxone or a corticosteroid [149, 151]. A randomized, double-blind, placebo-controlled trial administering TRH in the mid-1990s showed a statistically significant functional benefit in the National Acute Spinal Cord Injury Study (NASCIS) and in the Sunnybrook scales of partial, but not complete, spinal cord injured patients [152]. However, this study enrolled only 20 patients, and most were not available for prolonged follow-up [152].

Excitotoxicity Prevention

Cation homeostasis

Deregulation of cation homeostasis leading to uncontrolled activation of proteases and secretion of excitatory neurotransmitters, such as glutamate, may be an important process leading to excitotoxicity and heightened injury after CNS trauma and disease. It has been speculated that the loss of Na⁺ homeostasis, including the accumulation of intracellular Na⁺, serves as a critical initial pathophysiologic event of secondary neurologic spinal cord injury [153–155]. Local injection with the Na⁺ channel blocker tetrodotoxin (TTX) in a spinal contusion rat model resulted in reduced spinal cord white matter loss, a reduction in lesion diameter, and improvement in locomotor function [156]. However, since systemic delivery of TTX is impractical due to its high toxicity, Na⁺ channel blockers with reduced adverse effect profiles would be necessary for human trials.

The anticonvulsant riluzole has shown promise in a rat thoracic compression model by largely restoring somatosensory evoked potentials to levels near that of uninjured control animals and to have reduced the spinal infarct area by over 50% compared to vehicle-treated controls [157].

In addition to riluzole, the sodium channel blockers phenytoin, an anti-epileptic drug that disrupts glutamate release, and mexiletine, a class 1B anti-arrhythmic, have also shown promise in animal models of spinal injury [158]. A phase III clinical trial using riluzole in patients with ALS found only modest improvements in survival [159]. However, this treatment has received Health Canada regulatory approval. A prospective, multicenter phase I trial demonstrated that riluzole for cervical injuries may be beneficial for enhancing the progression of impairment grades [160].

Blockade of cation-dependent, including Ca²⁺ and K⁺, activation of destructive proteases such as calpain and the prevention of pre-synaptic glutamate release thereby limiting neural excitotoxicity has provided an additional avenue for ion regulation and homeostasis management of neurologic insult. Nimodipine, a dihydropyridine L-type voltage-gated calcium channel blocker, has shown promise

in suppressing cerebral vasospasm after cerebrovascular insult and may also provide clinical improvement in Glasgow coma score values after traumatic brain injury [161, 162]. Spinal cord injury studies evaluating nimodipine have provided mixed results, with a few trials finding improvement in CNS blood flow and enhancement of motor axon regenerative growth [163–165]. Others, including a human clinical trial, found no benefit to evoked potential recovery, spinal cord blood flow, or functional recovery in ASIA scoring [166–169]. Alternatively, use of the potassium-channel blocker 4-aminopyridine, Ampyra, has shown great promise in improving ambulation in patients with multiple sclerosis, although significant adverse effects, including vertigo and paresthesias, have been noted [170]. Treatment with 4-aminopyridine in both pre-clinical and clinical trials has demonstrated a robust ability to improve axonal conduction block [171–173], although most of the benefits in functional recovery have come from decreased spasticity [3, 173].

Glutamate regulation

Glutamate is an endogenous excitatory neurotransmitter. Direct disruption of its release and activity has shown potential in ameliorating neuronal excitotoxicity and cell death after SCI. The non-competitive excitatory N-methyl-d-aspartate (NMDA) receptor antagonist, gacyclidine (GK-11) showed early promise in restoring function while having a modest adverse effect profile in rat SCI models [174, 175]. However, a phase II clinical trial administering gacyclidine within 2 hours of injury [176] resulted in minimal benefit, with long-term primary outcome measures not attained [165].

Regulation of Scar Formation

After injury, the CNS undergoes physical and chemical alterations, including formation of the glial scar to improve blood–brain barrier integrity and minimize the spread of infection, inflammation, and propagation of cellular damage [14]. Chondroitin sulfate proteoglycans (CSPGs), which play important roles in developmental organization of the central nervous system and in the maintenance and plasticity of synaptic connections as

perineural nets in adulthood, are secreted by activated astrocytes and act as potent inhibitors to axon outgrowth after CNS injury within the glial scar [13]. Enzymatic cleavage of CSPGs using chondroitinase ABC (ChABC) promoted axon outgrowth in vitro, restored locomotor and proprioceptive behaviors in a dorsal columns rat injury and stimulated functional recovery of diaphragm activity in a rat cervical hemisection study [177–179]. However, significant differences in levels of CSPG deposition between different mechanisms of SCI, in different mammalian models, and a divergence in the ability of regenerating axons to grow into the glial scar region based on CSPG patterns have created challenges in how best to translate these findings to human trials [180]. Additionally, ChABC is a bacterial-derived enzyme that loses activity at human physiologic temperatures. Although heat-stable versions are in development [181], they may cause adverse effects when delivered systemically. However, continuous intrathecal delivery may alleviate some of those concerns. Delivery of ChABC using subcutaneous ports with subdural tubing proved safe and led to restored basic and skilled locomotor function in cats [182]. Trials administering ChABC in additional large animal models have not revealed any major adverse effects [183–185].

Cellular Transplantation

Cellular transplantation has become an active area of investigation for the treatment of traumatic and neurodegenerative CNS disorders. Transplantation of stem cells or autologous non-stem cells have been studied for their ability to replace lost neurons and glia, secrete grow-promoting trophic factors, and positively modulate the microenvironment through suppression of inflammation and scar formation [186–190]. Many cell types have shown promise in regulating at least one of the aforementioned functions, including Schwann cells, bone-marrow stromal cells, macrophages, T-cells, peripheral nerves, embryonic and adult neural stem and progenitor cells, mesenchymal stem cells, fate-restricted neural and glial precursor cells and olfactory ensheathing glial cells [188–190] (Fig. 22.5). The sheer diversity of cell types, delivery modalities, timing after injury and quantities and preparation of cells for transplantation

complicates effective evaluation of pre-clinical and clinical trials. Furthermore, concerns have arisen about the associated risks of cellular transplantation including tumorigenesis and aberrant axon sprouting and circuit formation leading to augmented dysfunction [188]. There is currently no consensus on which cell type will provide the most remarkable clinical outcomes, given that each provides individual strengths and weaknesses and the lack of standardized reporting of primary safety profiles from early human clinical trials [188, 190]. Endogenous and induced pluripotent stem cells are also gaining traction as viable agents for cellular transplantation, in hopes of eliminating the risk of graft rejection as well as alleviating ethical concerns about the use of embryonic stem cells.

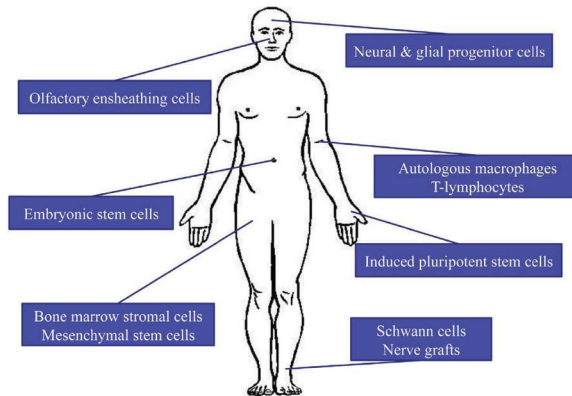


Figure 22.5 Types of cells collected for potential modulation of neural function or amelioration of cellular loss from disease or injury.

Alternative Interventions

Currently, no standard of care exists for the management of acute traumatic spinal cord injuries by promotion of active neural regeneration. Moreover, no standards are in place regarding the role, timing, and method of surgical intervention, including closed reduction using traction and open vertebral decompression [190, 191]. Other investigational treatments that have shown promise include induced moderate systemic hypothermia [192–197], oscillating field stimulation [198, 199], lesion-bridging polymer scaffolds [200, 201], and advanced rehabilitation efforts [3].

Management of analgesia after spinal cord injury is also a major area of clinical investigation, and one that is complicated by divergent origins and modalities of pain [202, 203].

Limits of the Model System for Studying Neuromodulation

Animal models have proven useful for revealing the CNS environment after injury and evaluating an abundance of therapeutic interventions for their discrete ability to impact cell death, axon outgrowth and sprouting, to regulate glial reactivity, modulate the immune response, and promote functional recovery. However, animal models have their limits. For example, they may not be able to recreate the intricacies of corresponding human conditions and often have divergent therapeutic effects from regenerative agents.

Human trials themselves suffer from significant heterogeneity of clinical presentations, small patient cohorts, and the substantial costs associated with conducting clinical trials. They also suffer from the protracted length of time necessary to delineate treatment benefits and poor standardization of trial management and transparency of results. Any intervention that promotes robust functional recovery in humans will likely need to be multifaceted and address several mechanisms that counteract the lack of natural adult neural regeneration. Such a multidimensional intervention may include biologic agents to prevent cell death and promote axon growth and sprouting, agents that induced mild hypothermia to minimize inflammation and injury dissemination, and electrical stimulation components or a direct interface with a machine or prosthetic device to optimize both the rate and comprehensiveness of neural regeneration and functional restoration.

CONCLUSION

The multiplicity of agents and techniques used in investigations of neural regeneration has promoted deeper understanding of both the challenges involved and the promise of focused neural modulation and regeneration. Modern advances in our

understanding of neural physiology and an enhanced appreciation for the pathophysiology underlying many traumatic injury states and neurologic disorders make targeted therapeutic interventions a viable objective. Focal delivery of cells, antibodies, vector-based agents, and small molecules offer the ability to modulate CNS function, augment neural activity, promote progenitor cell growth and differentiation, increase cellular survival, stimulate tumor cell death, and improve plasticity in CNS with substantial spatial and temporal control. Deep brain stimulation, covered in other chapters, has revolutionized how we can electrically target discrete regions of the brain, and techniques involving molecular and cellular interventions will provide a broader palette of options for modulating the nervous system to improve health and potentially even enhance existing theoretical limits of human cognitive abilities.

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